DRAFT REVISIONS FOR COMMENTS

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This draft revision contains revised monograph text for inclusion in the Indian Pharmacopoeia (IP). The content of this draft document is not final, and the text may be subject to further revisions prior to publication in the IP. This draft does not necessarily represent the decisions or the stated policy of the IP or Indian Pharmacopoeia Commission (IPC).

Manufacturers, regulatory authorities, health authorities, researchers, and other stakeholders are invited to provide their feedback and comments on this draft proposal. Manufacturers are also invited to submit samples of their products to the IPC to ensure that the proposed revised monograph adequately controls the quality of the product(s) they manufacture. Comments and samples received after the last date will not be considered by the IPC before finalizing the monograph.

Please send any comments you may have on this draft document to lab.ipc@gov.in, with a copy to Dr. Gaurav Pratap Singh (email: gpsingh.ipc@gov.in) before the last date for comments.

Document History and Schedule for the Adoption Process

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Further follow-up action as required.	

Index of Proposed Revisions

S. No.	Name of General Chapter/ Monograph	Details of Proposed Revision	Revision
1.	General Notices	Meaning of Terms	2.0
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3.	2.3.6. Related Foreign Steroids	Minor amendment	2.0
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5.	2.3.43. Water	Add sample quantity	3.0
6.	2.3.46. Assay of Insulins	Minor amendment	2.0
7.	2.3.48. Thiomersal	Minor amendment	2.0
8.	2.3.50. Fatty Acid Composition by Gas Chromatography	Method A: Chromatographic Conditions	1.0
9.	2.3.52. Assay of Folic Acid	Minor amendment	2.0
10.	2.4.13. Gas Chromatography	Minor amendment	2.0
11.	2.4.14. Liquid Chromatography	Minor amendment	2.0
12.	2.4.26. Solubility: Amorolfine Hydrochloride	Changed solubility	3.0
13.	4.2. General Reagents	Added 1. Acetylacetone 2. Acetylacetone Reagent 3. Iodine, xM	3.0
14.	4.5. Volumetric Reagents and Solutions	Disodium Edetate	1.0
15.	6.2. CONTAINERS	6.2.2. Glass Containers	3.0
16.	Parenteral Preparations	Extractable volume	2.0
17.	Tablets	Minor amendment	2.0
18.	Aceclofenac	Related substances upgraded	3.0
19.	Aciclovir	Related substances upgraded	2.0
20.	Albendazole Tablets	Dissolution Upgraded	2.0
21.	Aminophylline	Molecular formula and weight, Identification, Related substances (TLC to HPLC), Water and Assay (for theophylline) upgraded and Labelling added	3.0
22.	Aminophylline Injection	Identification, pH and Assay (for theophylline) upgraded and Related substances added	3.0
23.	Aminophylline Prolonged-release Tablets	Identification and Assay (for theophylline) upgraded and Related substances added	3.0
24.	Aminophylline Tablets	Identification and Assay (for theophylline) upgraded and Related substances added	3.0
25.	Amlodipine and Nebivolol Tablets	Dissolution Minor amendment	3.0
26.	Amlodipine and Olmesartan Medoxomil Tablets	Related Substances	1.0
27.	Amorolfine Hydrochloride	Identification, Related substances and Sulphated ash upgraded	3.0
28.	Amoxycillin Sodium	Minor amendment	3.0
29.	Amoxycillin and Potassium Clavulanate Injection	Minor amendment	3.0
30.	Amoxycillin and Potassium Clavulanate Oral Suspension	Minor amendment	3.0
31.	Amoxycillin and Potassium Clavulanate Tablets	Minor amendment	3.0

32.	Amphotericin B	Identification. B & rename "tetraenes" to "Limit of Amphotericin A"	3.0
33.	Anastrozole Tablets	Dissolution minor amendment	3.0
34.	Aprepitant	Heavy metals and Sulphated ash added	3.0
35.	Aripiprazole	Sulphated ash upgraded	1.0
36.	Aripiprazole Tablets	Dissolution Q limit upgraded	3.0
37.	Atenolol	Minor amendment	1.0
38.	Atracurium Besylate	Minor amendment	1.0
39.	Atorvastatin Tablets	Dissolution limit revised; Related substances upgraded	3.0
40.	Atropine Sulphate	Apoatropine and Foreign alkaloids and decomposition products deleted, Water limit revised, Related substances upgraded	3.0
41.	Bacitracin Zinc	Pyrogens upgrade	3.0
42.	Betahistine Tablets	Minor amendment	3.0
43.	Betamethasone Valerate Cream	Identification B and assay upgraded and Related substances added	3.0
44.	Betamethasone Valerate Ointment	Identification B and assay upgraded and Related substances added	3.0
45.	Bisacodyl Gastro-resistant Tablets	Minor amendment	3.0
46.	Budesonide	Related substances upgraded	3.0
47.	Bosutinib	Molecular Formula and weights, and water upgraded	3.0
48.	Aqueous Calamine Cream	Assay (Gravimetric to Titration) upgraded	3.0
49.	Calamine Ointment	Assay (Gravimetric to Titration) upgraded	3.0
50.	Capreomycin Injection	Minor amendment	3.0
51.	Carbamazepine	Identification B, Related substances and Assay upgraded	3.0
52.	Carbamazepine Tablets	Identification, Related substances and Assay upgraded	3.0
53.	Carboplatin	Related substances and Assay upgraded	3.0
54.	Carboxymethylcellulose Eye Drops	Assay upgraded	2.0
55.	Carvedilol	Related substances upgraded	3.0
56.	Carvedilol Tablets	Related substances upgraded	3.0
57.	Cefixime Tablets	Minor amendment	3.0
58.	Cefotaxime Sodium	Add Specific optical rotation	2.0
59.	Ceftriaxone Sodium	Description upgraded	3.0
60.	Ceftriaxone Injection	Description upgraded and minor amendment in Related substances	3.0
61.	Cefuroxime Axetil Tablets	Minor amendment	3.0
62.	Cefuroxime Sodium	Minor amendment	3.0
63.	Cefuroxime Injection	Minor amendment	3.0
64.	Cetostearyl Alcohol	Melting range deleted	3.0

65.	Cetyl Alcohol	Melting range deleted	3.0
66.	Chloramphenicol Ear Drops	Identification A upgraded	3.0
67.	Chlorpheniramine Maleate	Identification B, Related substances (TLC to HPLC) and Assay upgraded, Optical Rotation added and pH deleted	3.0
68.	Cilostazol Tablets	Identification A upgraded	3.0
69.	Ciprofloxacin	Identification B, Related substances upgraded and Fluoroquinolonic acid deleted	3.0
70.	Ciprofloxacin Injection	Identification upgraded	3.0
71.	Ciprofloxacin Hydrochloride	Identification B, Related substances upgraded and Fluoroquinolonic acid deleted	3.0
72.	Ciprofloxacin Eye Drops	Related substances added and assay upgraded	3.0
73.	Ciprofloxacin Tablets	Identification B deleted, Related substances added and assay upgraded	3.0
74.	Cisplatin Injection	Trichloroammineplatinate and Transplatin. deleted, and Related substances added	3.0
75.	Cisplatin for Injection	Trichloroammineplatinate and Transplatin deleted, and Related substances added	3.0
76.	Clarithromycin	Heavy metals upgraded and Sulphated ash added	3.0
77.	Clindamycin Palmitate Hydrochloride Oral Suspension	Minor amendment	3.0
78.	Clobetasol Propionate	Related substances and Assay upgradation	2.0
79.	Clobetasol Cream	Identification and Assay upgradation	2.0
80.	Clobetasol Ointment	Identification and Assay upgradation	2.0
81.	Clonazepam	Related substances and Assay upgraded and Clonazepam related compound C added	3.0
82.	Clonazepam Injection	Identification, Related substances (TLC to HPLC) and Assay (UV to HPLC) upgraded and Usual strength added	3.0
83.	Clonazepam Tablets	Identification, Related substances and Assay upgraded	3.0
84.	Clonidine Hydrochloride	Minor amendment	3.0
85.	Clopidogrel and Aspirin Tablets	Synonym and labelling added, assay limit and related substances upgraded	3.0
86.	Clotrimazole	Identification, Related substances and Assay (Titration to HPLC) upgraded	3.0
87.	Clotrimazole Lotion	Minor amendment	3.0
88.	Copovidone	Minor amendment	1.0
89.	Cyclobenzaprine Tablets	Minor amendment	1.0
90.	Cyproheptadine Hydrochloride	Assay (Titration to HPLC) upgraded	3.0
91.	Cyproheptadine Syrup	Identification upgraded and Labelling added	3.0
92.	Cyproheptadine Tablets	Storage and Labelling added	3.0

93.	Dicyclomine Tablets	Minor amendment	3.0
94.	Dithranol Ointment	Dihydroxyanthracene and Dihydroxyanthraquinone deleted, Impurity B and C and Impurity D added	3.0
95.	Docetaxel Anhydrous	Minor amendment	3.0
96.	Docetaxel Trihydrate	Minor amendment	3.0
97.	Docusate Tablets	Minor amendment	3.0
98.	Dolutegravir Tablets	Minor amendment	3.0
99.	Doxepin Hydrochloride	Minor amendment	3.0
100.	Doxepin Capsules	Minor amendment	3.0
101.	Duloxetine Hydrochloride	Minor amendment	3.0
102.	Dutasteride	Water upgraded	3.0
103.	Escitalopram Oxalate	Minor amendment	3.0
104.	Esomeprazole Gastro-resistant Tablets	Minor amendment	3.0
105.	Ethanolamine	Identification upgraded	3.0
106.	Anaesthetic Ether	Identification added	3.0
107.	Ethinyloestradiol Tablets	Dissolution added	3.0
108.	Ethosuximide Capsules	Identification and assay upgraded, Dissolution and Limit of 2-Ethyl-2-Methylsuccinic Acid added	**3.0**
109.	Fenofibrate Capsules	Minor amendment	**3.0**
110.	Finasteride	Sulphated ash added	**3.0**
111.	Fluconazole	Identification, Related substances and Assay (titration to HPLC) upgraded	**3.0**
112.	Fluconazole Capsules	Related substances upgraded	**3.0**
113.	Fluconazole Oral Suspension	Minor amendment	**3.0**
114.	Fluconazole Tablets	Related substances upgraded	**3.0**
115.	Fluocinolone Acetonide	Molecular formula and weight, and LOD upgraded	**3.0**
116.	Fluphenazine Decanoate	Minor amendment	**3.0**
117.	Frusemide	Identification, Related substances and Assay (titration to HPLC) upgraded	**3.0**
118.	Frusemide Injection	Identification, Related substances and Assay (UV to HPLC) upgraded	**3.0**
119.	Frusemide Tablets	Identification, Related substances and Assay (UV to HPLC) upgraded	**3.0**
120.	Gelatin	Minor amendment	**3.0**
121.	Gemifloxacin Tablets	Minor amendment	**3.0**
122.	Glimepiride	Minor amendment	**2.0**
123.	Glyceryl Trinitrate Tablets	Minor amendment	**3.0**
124.	Homatropine Methylbromide	Identification upgraded and Related substances minor amendments	**1.0**
125.	Hydrochlorothiazide	Minor amendment	**3.0**
126.	Hydroxyprogesterone Hexanoate	Minor amendment	**3.0**
127.	Hyoscine Butylbromide Injection	Identification upgraded	**3.0**
128.	Hyoscine Butylbromide Tablets	Identification upgraded	**3.0**
129.	Imipramine Tablets	Minor amendment	**3.0**
130.	Isoprenaline Sulphate	Minor amendment	**3.0**

131.	Ketorolac Tromethamine	Minor amendment	**3.0**
132.	Levofloxacin Injection	Minor amendment	**3.0**
133.	Levosalbutamol Hydrochloride	Identification upgraded	**3.0**
134.	Levosalbutamol Sulphate	Minor amendment	**3.0**
135.	Linezolid	Specific optical rotation changes to Enantiomeric purity, Related substances and Assay upgraded	**3.0**
136.	Linezolid Tablets	Related substances upgraded	**3.0**
137.	Loperamide Hydrochloride	Identification upgraded	**3.0**
138.	Loratadine Tablets	Dissolution added	**3.0**
139.	Lorazepam	Related substances upgraded	**3.0**
140.	Luliconazole	Structure and IUPAC name upgraded	**1.0**
141.	Magnesium Stearate	Minor amendment	**3.0**
142.	Mannitol	Related substances added, Sorbitol deleted and assay upgraded	**3.0**
143.	Mercaptopurine	Minor amendment	**1.0**
144.	Mesalazine	Minor amendment	**3.0**
145.	Mesalazine Prolonged-release Tablets	Minor amendment	**3.0**
146.	Metformin Hydrochloride	Related substances upgraded	**2.0**
147.	Metformin Oral Solution	Minor amendment	**2.0**
148.	Metformin Hydrochloride Prolonged-release Tablets	Related substances and Assay upgraded	**2.0**
149.	Metformin Tablets	Identification, Related substances and Assay upgraded	**2.0**
150.	Methadone Tablets	Minor amendment	**3.0**
151.	Methotrexate	Minor amendment	**3.0**
152.	Methotrexate Injection	Identification upgraded	**3.0**
153.	Methotrexate Tablets	Identification upgraded	**3.0**
154.	Methylprednisolone Tablets	Minor amendment	**3.0**
155.	Metoclopramide Tablets	Minor amendment	**3.0**
156.	Metronidazole Benzoate	Identification and Assay upgraded	**3.0**
157.	Mitiglinide Calcium Dihydrate	Minor amendment	**3.0**
158.	Mometasone Furoate	Identification, Related substances and Assay (UV to HPLC) upgraded	**3.0**
159.	Mometasone Aqueous Nasal Spray	Identification, Related substances (TLC to HPLC) and Assay upgraded	**3.0**
160.	Mometasone Cream	Identification, Related substances and Assay upgraded	**3.0**
161.	Mometasone Ointment	Identification and Assay upgraded, Related substances added	**3.0**
162.	Montelukast Sodium	Minor amendment	**3.0**
163.	Montelukast Tablets	Minor amendment	**3.0**
164.	Morphine Injection	Minor amendment	**3.0**
165.	Multiple Electrolytes and Dextrose Injection Type I	Minor amendment	**3.0**
166.	Multiple Electrolytes and Dextrose Injection Type II	Minor amendment	**3.0**
167.	Multiple Electrolytes and Dextrose Injection Type V	Minor amendment	**3.0**
168.	Multiple Electrolytes Injection Type VI	Minor amendment	**3.0**
169.	Naltrexone Hydrochloride	Related substances upgraded	**1.0**
170.	Norfloxacin	Minor amendment	**3.0**
171.	Norfloxacin Tablets	Related substances added	**3.0**

172.	Oleic Acid	Loss on ignition upgraded	**1.0**
173.	Olmesartan Medoxomil and Hydrochlorothiazide Tablets	Related substances upgraded	**1.0**
174.	Olopatadine Ophthalmic Solution	Minor amendment	**3.0**
175.	Omeprazole	Related substances upgraded	**3.0**
176.	Omeprazole Gastro-resistant Capsules	Related substances added and assay upgraded	**3.0**
177.	Ondansetron Tablets	Minor amendment	**1.0**
178.	Orphenadrine Hydrochloride	Minor amendment	**3.0**
179.	Oxcarbazepine	Related substances upgraded	**3.0**
180.	Oxcarbazepine Tablets	Related substances upgraded	**3.0**
181.	Oxybutynin Tablets	Identification upgraded	**2.0**
182.	Pantoprazole Sodium	Minor amendment	**1.0**
183.	Pantoprazole Gastro-resistant and Domperidone Prolonged-release Capsules	Minor amendment	**3.0**
184.	Parecoxib Sodium	Minor amendment	**3.0**
185.	Paroxetine Prolonged-release Tablets	Minor amendment	**1.0**
186.	Phenindione	Identification, Related substances (TLC to HPLC) and Assay (Titration to HPLC) upgraded	**3.0**
187.	Phenindione Tablets	Identification, Related substances (TLC to HPLC) and Assay (UV to HPLC) upgraded	**3.0**
188.	Phenylephrine Hydrochloride	Identification, Related substances and Assay upgraded	**3.0**
189.	Phenylephrine Eye Drops	Identification and Related substances (TLC to HPLC) upgraded	**3.0**
190.	Phenylephrine Injection	Identification, Related substances (TLC to HPLC) and Assay (UV to HPLC) upgraded	**3.0**
191.	Phenytoin Capsules	Related substances (TLC to HPLC) and Assay (Titration to HPLC) upgraded	**3.0**
192.	Phenytoin Tablets	Related substances (TLC to HPLC) and Assay (Titration to HPLC) upgraded	**3.0**
193.	Piroxicam	Identification, Related substances, Heavy metals, water and Assay upgraded and Limit of piroxicam related compound B added	**3.0**
194.	Pitavastatin Calcium	Minor amendment	**1.0**
195.	Prazosin Hydrochloride	Minor amendment	**3.0**
196.	Prazosin Tablets	Minor amendment	**3.0**
197.	Prednisolone	Identification, Related substances and Assay (UV to HPLC) upgraded	**3.0**
198.	Prednisolone Acetate	Minor amendment	**3.0**
199.	Prednisone Tablets	Minor amendment	**3.0**
200.	Prochlorperazine Maleate	Minor amendment	**3.0**
201.	Progesterone	Related substances and Assay (UV to HPLC) upgraded	**3.0**
202.	Progesterone Injection	Related substances added and Assay (UV to HPLC) upgraded	**3.0**
203.	Promethazine Hydrochloride	Identification, Related substances (TLC to HPLC) and Assay (Titration to HPLC) upgraded	**3.0**
204.	Promethazine Injection	Identification, Related substances and Assay (UV to HPLC) upgraded	**3.0**

205.	Promethazine Syrup	Identification and Assay (UV to HPLC) upgraded and Related substances added	**3.0**
206.	Promethazine Tablets	Identification, Related substances (TLC to HPLC) and Assay (UV to HPLC) upgraded and Dissolution added	**3.0**
207.	Propranolol Hydrochloride	Identification, Related substances and Assay (Titration to HPLC) upgraded	**3.0**
208.	Propranolol Prolonged-release Capsules	Identification, Related substances and Assay (UV to HPLC) upgraded	**3.0**
209.	Propranolol Injection	Identification, Related substances and Assay (UV to HPLC) upgraded	**3.0**
210.	Propranolol Tablets	Identification, Related substances and Assay (UV to HPLC) upgraded	**3.0**
211.	Pyrazinamide Tablets	Minor amendment	**3.0**
212.	Quinapril and Hydrochlorothiazide Tablets	Minor amendment	**3.0**
213.	Quinidine Sulphate	Minor amendment	**3.0**
214.	Quinine Bisulphate Tablets	Minor amendment	**3.0**
215.	Quinine Dihydrochloride Injection	Minor amendment	**3.0**
216.	Quinine Sulphate	Minor amendment	**3.0**
217.	Quinine Tablets	Minor amendment	**3.0**
218.	Ramipril	Related substances upgraded	**3.0**
219.	Ramipril Capsules	Related substances added	**3.0**
220.	Ramipril Tablets	Related substances added	**3.0**
221.	Ropinirole Prolonged-release Tablets	Minor amendment	**3.0**
222.	Ropinirole Tablets	Minor amendment	**3.0**
223.	Rupatadine Fumarate	Related substances, Assay, sulphated ash and LOD upgraded	3.0
224.	Salbutamol	Optical rotation, Impurity J added and Related substances upgraded	3.0
225.	Salbutamol Sulphate	Optical rotation and Related substances upgraded	3.0
226.	Salbutamol Injection	Salbutamol ketone added and Related substances and Assay (UV to HPLC) upgraded	3.0
227.	Sertraline Tablets	Minor amendment	3.0
228.	Simvastatin	Minor amendment	3.0
229.	Simvastatin Tablets	Related substances upgraded	3.0
230.	Sitagliptin Tablets	Minor amendment	1.0
231.	Sulphamethoxazole	Identification, Related substances and Assay (titration to HPLC) upgraded	3.0
232.	Telmisartan Tablets	Minor amendment	1.0
233.	Tamsulosin Hydrochloride	Related substances upgraded	3.0
234.	Tapentadol Hydrochloride	SOR change to Enantiomeric purity, Related substances and Assay upgraded	3.0
235.	Tenofovir Disoproxil Fumarate	Related substances upgraded	2.0
236.	Tenofovir Disoproxil Fumarate Tablets	Related substances upgraded	2.0
237.	Theophylline	Identification, Related substances and Assay upgraded, Labelling added and Light Absorption deleted	3.0

238.	Theophylline Injection	Related substances added and Assay upgraded	3.0
239.	Theophylline Prolonged-release Tablets	Related substances (TLC to HPLC) and Assay upgraded	3.0
240.	Tobramycin Sulphate	Assay and Water limit upgraded	1.0
241.	Tolnaftate	Minor amendment	3.0
242.	Topiramate	Minor amendment	3.0
243.	Topotecan Injection	Minor amendment	3.0
244.	Tranexamic Acid	Minor amendment	3.0
245.	Travoprost Eye Drops	pH upgraded and Labeling added	1.0
246.	Trimetazidine Hydrochloride	Minor amendment	3.0
247.	Tubocurarine Chloride	Minor amendment	3.0
248.	Ursodeoxycholic Acid	Impurity C (TLC to HPLC), Related substances upgraded	3.0
249.	Ursodeoxycholic Acid Tablets	Dissolution and Related substances upgraded, and Impurity C added	3.0
250.	Valacyclovir Tablets	Minor amendment	3.0
251.	Vancomycin Hydrochloride	Identification upgraded	3.0
252.	Vancomycin Capsules	Vancomycin B and Related substances added, Identification upgraded	3.0
253.	Sterile Water for Inhalation	Minor amendment	1.0
254.	Sterile Water for Injections	Minor amendment	1.0
VITAMINS, MINERALS, AMINO ACIDS, FATTY ACIDS ETC.			
255.	Nicotinic Acid	Identification, Related substances and Assay (titration to HPLC) upgraded	3.0
VETERINARY PRODUCTS			
256.	Inositol	Revised monograph	1.0
257.	Meloxicam Injection	Related substances and Assay upgraded	3.0

General Notices

Page. 12, 1286, 3000 and 4794
Meaning of Terms
Insert before **Label**
Ignite. Unless otherwise stated, ignite at a temperature 800±25°.

Page 14,
Insert before **Residual Solvents**

Impurities
Monographs may provide tests to detect and to control all known and potential impurities in the article. Non monograph tests and acceptance criteria suitable for detecting and controlling impurities that may result from a change in the processing methods or that may be introduced from external sources should be employed in addition to the tests provided in the individual monograph. The details on control of impurities are stated under chapter 5.5. Impurities. Nitrosamine impurities in the article, where reasonably expected to be present, are to be monitored and controlled as per the guidance stated under chapter 5.11. Nitrosamine Impurities.

Insert before **Test Methods**
Elemental Impurities. The requirements, guidance and information on control of elemental impurities are stated under chapter 5.10. Elemental Impurities. All IP articles are subject to relevant control of elemental impurities, even when no test is specified in the individual monograph. If any specific element is used during production, it must be of suitable quality. In addition, the toxicity of each element shall be taken into consideration and the elemental impurities should be limited according to the principles defined and the requirements specified in Chapter 5.10. Elemental Impurities should be tested using the general methods presented therein or other suitable methods.

2.3.6. Related Foreign Steroids. Page 170
Reference solution (b). Line 2 and 3
Change **from**: *prednisolone RS*, *prednisone RS* and *cortisone RS*
to: *prednisolone IPRS*, *prednisone IPRS* and *cortisone IPRS*

Reference solution (c). Line 2 and 3
Change **from**: *prednisolone acetate RS*, *prednisone RS*, *cortisone RS*, and *desoxycortone acetate RS*
to: *prednisolone acetate IPRS*, *prednisone IPRS*, *cortisone IPRS*, and *desoxycortone acetate IPRS*

2.3.42. Assay of Vitamin D. Page 189
Standard preparation of vitamin D. Line 2
Change **from**: *ergocalciferol RS* or *cholecalciferol RS*
to: *ergocalciferol IPRS* or *cholecalciferol IPRS*

2.3.43. Water. Page 190
Method 1. Titrimetric Method
Para before **Method A**
Change **from**: Follow Method A unless otherwise directed.
to: *NOTE- Unless otherwise specified in the individual monograph, transfer an accurately weighed or measured amount of the substance under examination estimated to contain 2-25 mg of water, to the titration vessel.*
Use Method A, unless otherwise specified in the individual monograph.

2.3.46. Assay of Insulins. Page 194
Method A. *Reference solution (a)*, para 2
Line 3 and 4
Change **from**: *human insulin RS* or *porcine insulin RS,* or of *bovine insulin RS,*
to: *human insulin IPRS* or *porcine insulin IPRS,* or *bovine insulin IPRS,*

Line 6

Change **from**: *bovine insulin RS*
to: *bovine insulin IPRS*

Line 8
Change **from**: *porcine insulin RS*
to: *porcine insulin IPRS*

Reference solution (c), line 2
Change **from**: *human insulin RS*
to: *human insulin IPRS*

Reference solution (d), line 2
Change **from**: *porcine insulin RS*
to: *porcine insulin IPRS*

After Chromatographic system, last para, line 5 and 6
Change **from**: *bovine insulin RS*, *porcine insulin RS* or *human insulin RS*,
to: *bovine insulin IPRS*, *porcine insulin IPRS* or *human insulin IPRS*,

2.3.48. Thiomersal. Page 199

Method A. Line 12
Change **from**: *thiomersal*
to: *thiomersal IPRS*

Method B. Last line
Change **from**: *Thiomersal* RS.
to: *thiomersal IPRS*

2.3.50. Fatty Acid Composition by Gas Chromatography. Page 200

Method A. Chromatographic system
Change **to**: Chromatographic system
– a capillary column 10-30 m x 0.2-0.8 mm, packed with fused silica coated with macrogol 20,000 (film thickness 0.1-0.5 µm) or another suitable stationary phase,
– temperature:
– column. in isothermal conditions, 160°-200°, according to the length and type of column used (200° for a column 30 m long and coated with a layer of macrogol 20,000); if a linear temperature programming is necessary, raise the temperature of the column at a rate of 3° per minute from 170° to 230°,
– inlet port and detector at 250°,
– flame ionization detector,
– flow rate: 1.3 ml per minute (for a column of internal diameter- 0.32mm) using helium or hydrogen as carrier gas,
– split ratio: 1:100 or less, according to the internal diameter of the column used (1:50 when internal diameter = 0.32 mm),
- injection volume: 1µl.

2.3.52. Assay of Folic Acid. Page 203

Reference solution (a). Line 1 and 2
Change **from**: *Folic Acid RS*,
to: *folic acid IPRS*,

2.4.13. Gas Chromatography. Page 232

Insert before **Adjustment of chromatographic conditions**
NOTE−Retention times and relative retentions may be provided in monographs for information purposes only, unless otherwise stated in the monograph. There are no acceptance criteria applied to relative retentions.

2.4.14. Liquid Chromatography. Page 235

Insert before **Adjustment of chromatographic conditions**
NOTE−Retention times and relative retentions may be provided in monographs for information purposes only, unless otherwise stated in the monograph. There are no acceptance criteria applied to relative retentions.

2.4.26. Solubility. Page 264
Page 266
Amorolfine Hydrochloride
Change **from**: Soluble in *water* and *ethanol*.
to: Soluble in *methanol* and in *methylene chloride*; slightly soluble in *water*.

4.2. General Reagents. Page 1066

Insert before **N-Acetylneuraminic acid**
Acetylacetone; 2,4-Pentanedione: $C_5H_8O_2$ = 100.1

Colourless or slightly yellow, easily flammable liquid, freely soluble in *water*; miscible with *acetone*, with *ethanol (95 per cent)* and with *glacial acetic acid*. $n\frac{20}{D}$, 1.452 to 1.453; bp, about 138° to 140°.

Acetylacetone Reagent. To 100 ml of *ammonium acetate solution* add 0.2 ml of *acetylacetone*.

Iodine, x M. Page 1097
Line 2 and 3
Change **from**: Dissolve 400 x g of *potassium iodide* in the minimum amount of *water*, add 260 x g of *iodine*,
to: Dissolve 720 x g of *potassium iodide* in the minimum amount of *water*, add 280 x g of *iodine*,

4.5. Volumetric Reagents and Solutions
Page 1145
Disodium Edetate, 0.1 M. Para 2, last line
Change **from**: green.
to: blue.

6.2. CONTAINERS. Page 1228
6.2.2. Glass Containers. Page 1263
Hydrolytic resistance. Test 1
Para 4, line 6
Change **from**: Table 2
to: Table 4

Parenteral Preparations. Page 1337
Injections
Extractable volume

Change **to**: **Extractable volume**

Suspensions and emulsions are shaken before withdrawal of the contents and before the determination of the density. Oily and viscous preparations may be warmed according to the instructions on the label, if necessary, and thoroughly shaken immediately before removing the contents. The contents are then cooled to 20-25° before measuring the volume.

Single-dose containers. Determine an appropriate number of containers to be tested, based on the number of units available and a suitable statistical approach. Following the instructions on the label, extract the total contents of each container selected into a suitable, dry syringe fitted with a suitable needle, e.g. a 21-gauge needle not less than 2.5 cm in length. Expel any air bubbles from the syringe and needle, taking care not to spill out any product. Then discharge the contents of the syringe without emptying the needle into a calibrated dry cylinder (graduated to contain rather than to deliver the designated volumes) of such a capacity that the volume to be measured occupies at least 40 per cent of its graduated volume. Alternatively, the volume of the contents in milliliters may be calculated as the mass in grams divided by the density.

The volume in each container tested is not less than the nominal volume.

Multidose containers. For injections in multidose containers labelled to yield a specific number of doses of a stated volume, select one container and proceed as directed for single-dose containers using the same number of separate syringe assemblies as the number of doses specified.

The volume extracted into each syringe is such that it delivers not less than the dose stated on the label.

Cartridges and prefilled syringes

Determine an appropriate number of containers to be tested, based on the number of units available and a suitable statistical approach. If necessary, fit the containers with the accessories required for their use (needle, piston and syringe) and transfer the entire content of each container, without emptying the needle in a dry tared beaker by slowly and continuously depressing the piston. Calculate the volume in milliliters calculated as the mass in grams divided by density.

The volume measured in each of the container tested is not less than the nominal volume.

Large-volume Parenterals

Determine an appropriate number of containers to be tested, based on the number of units available and a suitable statistical approach. Transfer the contents of the container into a calibrated dry cylinder of such a capacity that the volume to be measured occupies at least 40 per cent of its nominal volume. Measure the volume transferred. Alternatively, the volume of the contents in millilitres may be calculated as the mass in grams divided by the density.

The volume in each container tested is not less than the nominal volume.

Tablets. Page 1342

Gastro-resistant Tablets. Page 1345

Disintegration. Lines1 to 3

Change **from**: If the tablet has a soluble external coating, immerse the basket in water at room temperature for 5 minutes.

to: Place 1 tablet in each of the 6 tubes of the basket. If the tablets are not sugar-coated, proceed to the Acid stage. If testing tablets that have a soluble external sugar coating, immerse the basket in water at room temperature for 5 minutes.

Aceclofenac. Page 1367

Related substances

Change **to**: **Related substances**. Determine by liquid chromatography (2.4.14).

NOTE — Prepare the solutions immediately before use.

Solvent mixture. 30 volumes of mobile phase A and 70 volumes of mobile phase B.

Test solution. Dissolve 50 mg of the substance under examination in the solvent mixture and dilute to 25.0 ml with the solvent mixture.

Reference solution (a). A 0.043 per cent w/v solution of *diclofenac sodium IPRS (aceclofenac impurity A)* in the solvent mixture.

Reference solution (b). A 0.04 per cent w/v solution of *aceclofenac IPRS* in the solvent mixture.

Reference solution (c). Mix 1.0 ml, each of reference solution (a) and reference solution (b) to 100.0 ml with the solvent mixture.

Reference solution (d). A 0.04 per cent w/v solution of *aceclofenac impurity F IPRS* in the solvent mixture.

Reference solution (e). A 0.02 per cent w/v solution of *aceclofenac impurity H IPRS* in the solvent mixture.

Reference solution (f). Mix 1.0 ml, each of, reference solution (b), (d), and (e) and dilute to 100.0 ml with the solvent mixture.

Reference solution (g). A 0.002 per cent w/v solution of *aceclofenac impurity I IPRS* in the solvent mixture. Dilute 1.0 ml of the solution to 10.0 ml with the solvent mixture.

Reference solution (h). A solution containing 0.2 per cent w/v, each of, *aceclofenac impurity B IPRS, aceclofenac impurity C IPRS, aceclofenac impurity D IPRS, aceclofenac impurity E IPRS and aceclofenac impurity G IPRS* in the solvent mixture.

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with endcapped octadecylsilane bonded to porous silica (5 µm),
- column temperature: 40°,
- mobile phase: A. a 0.11 per cent w/v solution of *orthophosphoric acid*, adjusted to pH 7.0 with *1M sodium hydroxide*,

B. a mixture of 90 volumes of *acetonitrile* and 10 volumes of *water*,

- a gradient programme using the conditions given below,
- flow rate: 1ml per minute,
- spectrophotometer set at 275 nm,
- injection volume: 10 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	70	30
25	50	50
30	20	80
50	20	80
50.1	70	30
55	70	30

Name	Relative retention time
Aceclofenac impurity A[1]	0.8
Aceclofenac (Retention time: about 11minutes)	1.0
Aceclofenac impurity G[2]	1.3
Aceclofenac impurity H[3]	1.5
Aceclofenac impurity I[4]	2.3
Aceclofenac impurity D[5]	3.1
Aceclofenac impurity B[6]	3.2
Aceclofenac impurity E[7]	3.3
Aceclofenac impurity C[8]	3.5
Aceclofenac impurity F[9]	3.7

[1][2-[(2,6-dichlorophenyl-amino]phenyl]acetic acid (diclofenac),
[2][[[[[2-[(2,6-dichlorophenyl)amino]phenyl]acetyl]oxy]acetyl]oxy]acetic acid (acetic aceclofenac),
[3][[[[[[[2-[(2,6-dichlorophenyl)amino]phenyl acetyl]oxy]acetyl]oxy]acetic acid (diaceticaceclofenac),
[4]1-(2,6-dichlorophenyl)-1,3-dihydro-2*H*-indol-2-one.
[5]methyl [[[2-[(2,6-dichlorophenyl)amino]phenyl]acetyl]oxy]acetate (methyl ester of aceclofenac),
[6]methyl [2-[(2-6-dichlorophenyl)amino]phenyl]acetate (methyl ester of diclofenac),
[7] ethyl [[[2-[(2,6-dichlorophenyl)amino]phenyl]acetyl]oxy]acetate (ethyl ester of aceclofenac),
[8]ethyl [2-[(2-6-dichlorophenyl)amino]phenyl]acetate (ethyl ester of diclofenac),
[9]benzyl [[[2-(2,6-dichlorophenyl)amino]phenyl]acetyl]oxy]acetate (benzyl ester of aceclofenac),

Inject reference solution (h) to identify the peaks due to aceclofenac impurity B, C, D, E and G.

Inject reference solution (c). The test is not valid unless the resolution between the peaks due to aceclofenac impurity A and aceclofenac is not less than 5.0.

Inject reference solution (c), (f), (g), and the test solution. In the chromatogram obtained with the test solution, the area of the any peak corresponding to aceclofenac impurity A is not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.2 per cent), the area of any peak corresponding to aceclofenac impurities B, C, D, E, and G, each of, is not more than the area of the aceclofenac peak in the chromatogram obtained with reference solution (f) (0.2 per cent), the area of any peak corresponding to aceclofenac impurity F is not more than the area of the corresponding peak in the chromatogram obtained with reference solution (f) (0.2 per cent), the area of any peak corresponding to aceclofenac impurity H is not more than 1.5 times the area of the corresponding peak in the chromatogram obtained with reference solution (f) (0.15 per cent), the area of any peak corresponding to aceclofenac impurity I is not more than 1.5 times the area of the corresponding peak in the chromatogram obtained with reference solution (g) (0.15 per cent), the area of any other secondary peak is not more than 0.5 times the area of the aceclofenac peak in the chromatogram obtained with reference solution (f) (0.1 per cent) and the sum of areas of all the secondary peaks is not more than 3.5 times the area of the aceclofenac peak in the chromatogram obtained with reference solution (f) (0.7 per cent). Ignore any peak with an area less than 0.25 times the area of the aceclofenac peak in the chromatogram obtained with reference solution (f) (0.05 per cent).

Aciclovir. Page 1374

Related substances Change **to**:
Related substances. Determine by liquid chromatography (2.4.14).

NOTE- Prepare the solutions immediately before use.

Solvent mixture. 20 volumes of *dimethyl sulphoxide* and 80 volumes of *water*.

Test solution. Dissolve 25 mg of the substance under examination in 5.0 ml of *dimethyl sulphoxide* and dilute to 25.0 ml with *water*.

Reference solution (a). A 0.001 per cent w/v solution of *acyclovir IPRS* in *dimethyl sulphoxide*. Dilute 1.0 ml of the solution to 10.0 ml with the solvent mixture.

Reference solution (b). Dissolve 5 mg of *aciclovir for system suitability AIPRS* (containing impurities B, J, K, N, O and P) in 1 ml of *dimethyl sulphoxide* and dilute to 5 ml with *water*.

Reference solution(c). Dissolve the content of a vial of *aciclovir for impurity C identification IPRS* in 200 µl of *dimethyl sulfoxide* and dilute to 1 ml with *water*.

Reference solution(d). Dissolve the content of a vial of *aciclovir for impurity G identification IPRS* in 1 ml of reference solution (b).

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with end-capped octadecylsilane bonded to porous silica (5 µm),
- mobile phase: A. a mixture of 99 volumes of a buffer solution prepared by dissolving 3.48 g of *dipotassium hydrogen orthophosphate* in 1000 ml of *water*, adjusted to pH 3.1 with *orthophosphoric acid* and 1 volume of *acetonitrile*,
  B. a mixture of 50 volumes of a buffer solution prepared by dissolving 3.48 g of *dipotassium hydrogen orthophosphate* in 1000 ml of *water,* adjusted to pH 2.5 with *orthophosphoric acid* and 50 volumes of *acetonitrile*,
- a gradient programme using the conditions given below,
- flow rate: 1 ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 10 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	100	0
5	100	0
27	80	20
40	80	20
40.1	100	0
50	100	0

Name	Relative retention time	Correction factor
Aciclovir impurity B[1]	0.4	
Aciclovir impurity P[2]	0.7	
Aciclovir impurity C[3]	0.9	2.2
Aciclovir (Retention time: about 13 minutes)	1.0	
Aciclovir impurity N[4]	1.37	
Aciclovir impurity O[5] and Q[6]	1.42	
Aciclovir impurity J[7]	1.62	
Aciclovir impurity K[8] andR[9]	2.5	
Aciclovir impurity G[10]	2.6	

[1] 2-amino-1,7-dihydro-6*H*-purin-6-one (guanine),
[2] 2-amino-9-(2-hydroxyethyl)-1,9-dihydro-6H-purin-6-one,
[3] 2-amino-7-[(2-hydroxyethoxy)methyl]-1,7-dihydro-6Hpurin- e-one,
[4] unknown structure,
[5] unknown structure,
[6] mixture of 2-amino-9-[[2-(hydroxyethoxy)methoxy]methyl]-1,9-dihydro-6H-purin-6-one and 2-amino-9-[[2-(hydroxymethoxy)ethoxy]methyl]-1,9dihydro- 6H-purin-6-one,
[7] 9,9'-[ethane-1,2-diylbis(oxymelhylene)]bis(2-amino-1 ,9dihydro-6H-purin-6-one),
[8] 2,2'-(methylenediazanediyl)bis[9-[(2-hydroxyethoxy) methyl]-1 ,9-dihydro-6H-purin-6-one],
[9] 9,9'-[methylenebis(oxyethane-2,1-diyloxymethylene)]bis(2-amino-1,9-dihydro-6H-purin-6-one),
[10] 2-[(2-acetamido-6-oxo-1,6-dihydro-9H-purin-9-yl)methoxy]ethyl acetate.

Inject reference solution (c) and (d) to identify the peak due to aciclovir impurity C and peaks due to aciclovir impurity B, G, J, K, N, O and P, respectively.

Inject reference solution (c) and (d). The test is not valid unless the resolution between the peaks due to aciclovir impurity C and aciclovir is not less than 1.5 in the chromatogram obtained with reference solution (c) and between the peaks due to aciclovir impurity k and aciclovir impurity G is not less than 1.5 in the chromatogram obtained with reference solution (d).

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution the area of any peak corresponding to aciclovir impurity B is not more than 7 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.7 per cent), the area of any peak corresponding to aciclovir impurity J is not more than twice

the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent), the sum of areas of the peaks corresponding to acyclovir impurity K and R is not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent), the sum of areas of the peaks corresponding to acyclovir impurity O and Q is not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent), the area of any peak corresponding to acyclovir impurity C, N and P, each of, is not more than 1.5 times the area of principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent), the area of any other secondary peak is not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent), and the sum of the areas of all the secondary peaks is not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent). Ignore any peak with an area less than 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.03 per cent).

Albendazole Tablets. Page 1393

Dissolution. Change **to:**
Dissolution (2.5.2).
Apparatus No. 2 (Paddle),
Medium: 900 ml of *0.1 M hydrochloric acid* for 200 mg and *0.3 M hydrochloric acid* for 400 mg,
Speed and time. 50 rpm for 30 minutes.

Withdraw a suitable volume of the medium and filter, rejecting the first few ml of the filtrate. Dilute a suitable volume of the filtrate with the medium, if necessary. Measure the absorbance of the resulting solution at the maximum at about 291 nm (2.4.7). Calculate the content of $C_{12}H_{15}N_3O_2S$ in the medium from the absorbance obtained from a solution of known concentration of *albendazole IPRS,* prepared by dissolving in minimum quantity of *methanol* and diluted with the dissolution medium to obtain a solution having similar concentration as the test solution.

Q. Not less than 80 per cent of the stated amount of $C_{12}H_{15}N_3O_2S$.

Aminophylline. Page 1434

Insert before para 1
$(C_7H_8N_4O_2)2$, $C_2H_8N_2$. $2H_2O$ Mol. Wt. 456.5 (dihydrate)

Identification
Change **to**: **Identification**
A. Dissolve 0.5 g in 20 ml of *water*, add 1 ml of *3M hydrochloric acid* and filter. Reserve the filtrate for test C. Wash the precipitate with small portions of cold *water* and dry at 105° for 1 hour. On the residue, determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *theophylline IPRS* or with the reference spectrum of theophylline.

B. In the Assay of theophylline, the principal peak in the chromatogram obtained with test solution (b) corresponds to the peak in the chromatogram obtained with reference solution (a).

C. To the filtrate obtained in Identification A, add 0.5 ml of *benzene sulphonyl chloride* and 5 ml of *1M sodium hydroxide* to render alkaline. Shake by mechanical means for 10 minutes, add 5 ml of *3M hydrochloride acid* to acidify, chill, collect the precipitated disulphonamide of ethylenediamine. Wash with water, recrystallize from water and dry at 105° for 1 hour; the dried precipitate melts at 164° to 171° (2.4.21).

Related substances
Change **to**: **Related substances**. Determine by liquid chromatography (2.4.14).

Test solution (a). Dissolve 50 mg of the substance under examination in *water* and dilute to 50.0 ml with *water*.

Test solution (b). Dilute 5.0 ml of test solution (a) to 25.0 ml with *water*.

Reference solution (a). A 0.017 per cent w/v solution of *theophylline IPRS* in *water*.

Reference solution (b). A solution containing 0.0025 per cent w/v, each of, *caffeine IPRS*, *theophylline IPRS, theophylline related compound B IPRS, theophylline related compound C IPRS, theophylline related compound D IPRS* and *theophylline related compound F IPRS* in *water.* Dilute 1.0 ml of the solution to 25.0 ml with *water.*

Reference solution (c). Dissolve 21 mg of *theophylline IPRS* in 15 ml of *water,* with the aid of ultrasound, add 1.0 ml of a 0.0025 per cent w/v solution of *theophylline related compound F IPRS* in *water* and dilute to 25.0 ml with *water.*

Chromatographic system

- a stainless steel column 10 cm x 2.1 mm, packed with octadecylsilane bonded to porous silica (1.7 µm) (Such as Acquity UPLC BEH C18),
- column temperature: 40°,
- mobile phase: A. a buffer solution prepared by dissolving 770.8 mg of *ammonium acetate* in 800 ml with *water,* adjusted to pH 5.5 with *glacial acetic acid* and dilute to 1000 ml with *water,*
  B. *methanol,*
- a gradient programme using the conditions given below,
- flow rate: 0.4 ml per minute,
- spectrophotometer set at 270 nm,
- injection volume: 1 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	98	2
7	50	50
7.3	10	90
8.3	10	90
8.31	98	2
12	98	2

Name	Relative retention time
Theophylline related compound C[1]	0.36
Theophylline related compound B[2]	0.63
Theophylline related compound D[3]	0.69
Dimethyl uric acid[4]	0.76
Theobromine[5]	0.82
Theophylline	1.0
Theophylline related compound F[6]	1.09
Caffeine	1.20

[1]N-(6-Amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)formamide,
[2]3-Methyl-1H-purine-2,6-dione,
[3]N-Methyl-5-(methylamino)-1H-imidazole-4-carboxamide hydrochloride monohydrate,
[4]1,3-Dimethyl-7,9-dihydro-1H-purine-2,6,8(3H)-trione,
[5]3,7-Dihydro-3,7-dimethylpurine-2,6(1H)-dione,
[6]7-(2-Hydroxyethyl)-1,3-dimethyl-3,7-dihydro-1H-purine-2,6-dione.

Inject reference solution (b) and (c). The test is not valid unless the resolution between the peaks due to theophylline and theophylline related compound F is not less than 2.0 in the chromatogram obtained with reference solution (c) and the relative standard deviation for replicate injections is not more than 3.0 per cent, for each peak, in the chromatogram obtained with reference solution (b).

Inject reference solution (b) and test solution (a). In the chromatogram obtained with test solution (a), the area of any peak corresponding to caffeine, theophylline related compound B, C, D and F, each of, is not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.1 per cent), the area of any peak corresponding to dimethyl uric acid and theobromine, each of, is not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent),the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent) and the sum of the areas of all the secondary peaks is not more than 3 times the area of the principal peak in the chromatogram with reference solution (b) (0.3 per cent). Ignore any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Water

Change **to**: **Water** (2.3.43). Not more than 0.75 per cent (for anhydrous) and not more than 7.9 (for dihydrate), determined on 1.5 g dissolved in 50 ml of equal volumes of *chloroform* in *anhydrous methanol.*

Assay. *For theophylline —*

Change **to**: *For theophylline —* Determine by liquid chromatography (2.4.14), as described under Related substances with the following modifications.

Inject reference solution (a) and (c). The test is not valid unless the resolution between the peaks due to theophylline and theophylline related compound F is not less than 2.0 in the chromatogram obtained with reference solution (c) and the relative standard deviation for replicate injections is not more than 1.0 per cent in the chromatogram obtained with reference solution (a).

Inject reference solution (a)and test solution (b).

Calculate the content of theophylline, $C_7H_8N_4O_2$.

Insert at the end
Labelling. The label it to indicate whether it is anhydrous or hydrous and also to state the content of anhydrous theophylline.

Aminophylline Injection. Page 1435

Identification

Change **to**: **Identification**

A. Dilute a volume of injection containing 0.5 g of Aminophylline in 20 ml of *water,* add with constant strring, add 1 ml of *3M hydrochloric acid* or enough to completely precipitate the theophylline and filter. Reserve the filtrate for test C. Wash the precipitate with small portions of cold water and dry at 105° for 1 hour. On the residue, determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *theophylline IPRS* or with the reference spectrum of theophylline.

B. In the Assay of theophylline, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with reference solution (a).

C. To the filtrate obtained in Identification A, add 0.5 ml of *benzene sulphonyl chloride* and add 5 ml of *1M sodium hydroxide* to render alkaline. Shake by mechanical means for 10 minutes, add 5 ml of *3M hydrochloride acid* to acidify, chill, collect the precipitate disulphonamide to ethylenediamine, wash with water, recrystallize from water and drying at 105° for 1 hour; the dried precipitate melts at 164° to 171° (2.4.21).

pH

Change **from**: 8.8 to10.0.
to: 8.6 to 9.0.

Insert before **Bacterial endotoxins**

Related substances. Determine by liquid chromatography (2.4.14).

Test solution. Transfer a volume of injection containing 25 mg of anhydrous aminophylline to a 25-ml volumetric flask, dissolve and dilute to volume with *water*.

Reference solution (a). A 0.017 per cent w/v solution of *theophylline IPRS* in *water*.

Reference solution (b). A solution containing 0.0002 per cent w/v, each of, *theophylline IPRS* and *theophylline related compound D IPRS* in *water.*

Reference solution (c). Dissolve 21 mg of *theophylline IPRS* in 15 ml of *water*, with the aid of ultrasound, add 1 ml of a 0.0025 per cent w/v solution of *theophylline related compound F IPRS* in *water* and dilute to 25.0 ml with *water*

Chromatographic system

- a stainless steel column 10 cm x 2.1 mm, packed with octadecylsilane bonded to porous silica (1.7 µm) (Such as Acquity UPLC BEH C18),
- column temperature: 40°,
- mobile phase: A. a buffer solution prepared by dissolving 770.8 mg of *ammonium acetate* in 800 ml with *water,* adjusted to pH 5.5 with *glacial acetic acid* and dilute to 1000 ml with *water,*
  B. *methanol,*
- a gradient programme using the conditions given below,
- flow rate: 0.4 ml per minute,
- spectrophotometer set at 270 nm,
- injection volume: 1 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	98	2
7	50	50
7.3	10	90
8.3	10	90
8.31	98	2
12	98	2

Name	Relative retention time
Theophylline related compound C[1*]	0.36
Theophylline related compound B[2*]	0.63
Theophylline related compound D[3]	0.69
Dimethyl uric acid[4*]	0.76
Theobromine[5*]	0.82
Theophylline	1.0
Theophylline related compound F[6*]	1.09
Caffeine[*]	1.20

[*]Process impurity, included for identification only and not included in the calculation of total degradation products,
[1]N-(6-Amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)formamide,
[2]3-Methyl-1H-purine-2,6-dione,
[3]N-Methyl-5-(methylamino)-1H-imidazole-4-carboxamide hydrochloride monohydrate,
[4]1,3-Dimethyl-7,9-dihydro-1H-purine-2,6,8(3H)-trione,
[5]3,7-Dihydro-3,7-dimethylpurine-2,6(1H)-dione,
[6]7-(2-Hydroxyethyl)-1,3-dimethyl-3,7-dihydro-1H-purine-2,6-dione.

Inject reference solution (b) and (c). The test is not valid unless the resolution between the peaks due to theophylline and theophylline related compound F is not less than 2.0 in the chromatogram obtained with reference solution (c) and the relative standard deviation for replicate injections is not more than 3.0 per cent, for each peak, in the chromatogram obtained with reference solution (b).

Inject reference solution (b) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to theophylline related compound Dis not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.2 per cent),the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent)and the sum of the areas of all the secondary peaks is not more than 2.5 times the area of the principal peak in the chromatogram with reference solution (b) (0.5 per cent). Ignore any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Assay. *For theophylline —*
Change **to**: *For theophylline —* Determine by liquid chromatography (2.4.14), as described under Related substances with the following modifications.

Test solution. Transfer a volume of injection containing 8.5 mg of anhydrous aminophylline to a 50-ml volumetric flask, dissolve and dilute to volume with *water*.

Inject reference solution (a) and (c). The test is not valid unless the resolution between the peaks due to theophylline and theophylline related compound F is not less than 2.0 in the chromatogram obtained with reference solution (c) and the relative standard deviation for replicate injections is not more than 1.0 per cent in the chromatogram obtained with reference solution (a).

Inject reference solution (a) and the test solution.

Calculate the content of theophylline, $C_7H_8N_4O_2$ in the injection.

Aminophylline Prolonged- release Tablets. Page 1436

Identification

Change **to**: **Identification**

A. Disperse a quantity of the powdered tablets containing 0.5 g of Aminophylline with 20 ml of *water*, filter, add to the filtrate with constant stirring 1 ml of *3M hydrochloric acid*, allow to stand for a few minutes and again filter. Reserve the filtrate for test C. Wash the residue with small quantities of cold water, recrystallise from hot water and dry at 105°. On the residue, determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *theophylline IPRS* or with the reference spectrum of theophylline.

B. In the Assay of theophylline, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with reference solution (a).

C. To the filtrate obtained in Identification A, add 0.5 ml of *benzene sulphonyl chloride* and add 5 ml of *1M sodium hydroxide* to render alkaline. Shake by mechanical means for 10 minutes, add 5 ml of *3M hydrochloride acid* to acidify, chill, collect the precipitated disulphonamide to ethylenediamine and wash with *water.* Recrystallize the washed precipitate from water and drying at 105° for 1 hour; the dried precipitate melts at 164° to 171° (2.4.21).

Insert before **Other tests**
Related substances. Determine by liquid chromatography (2.4.14).

Test solution. Disperse a quantity of the powdered tablets containing 100 mg of anhydrous Aminophylline in 50 ml of *water*, with the aid of ultrasound for 30 minutes and dilute to 100.0 ml with *water*.

Reference solution (a). A 0.017 per cent w/v solution of *theophylline IPRS* in *water*.

Reference solution (b). A solution containing 0.0002 per cent w/v, each of, *theophylline IPRS* and *theophylline related compound D IPRS* in *water.*

Reference solution (c). Dissolve 21 mg of *theophylline IPRS* in 15 ml of *water,* with the aid of ultrasound, add 1 ml of a 0.0025 per cent w/v solution of *theophylline related compound F IPRS* in *water* and dilute to 25.0 ml with *water*

Chromatographic system

- a stainless steel column 10 cm x 2.1 mm, packed with octadecylsilane bonded to porous silica (1.7 µm) (Such as Acquity UPLC BEH C18),
- column temperature: 40°,
- mobile phase: A. a buffer solution prepared by dissolving 770.8 mg of *ammonium acetate* in 800 ml with *water,* adjusted to pH 5.5 with *glacial acetic acid* and dilute to 1000 ml with *water,*
  B. *methanol,*
- a gradient programme using the conditions given below,
- flow rate: 0.4 ml per minute,
- spectrophotometer set at 270 nm,
- injection volume: 1 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	98	2
7	50	50
7.3	10	90
8.3	10	90
8.31	98	2
12	98	2

Name	Relative retention time
Theophylline related compound C[1*]	0.36
Theophylline related compound B[2*]	0.63
Theophylline related compound D[3]	0.69
Dimethyl uric acid[4*]	0.76
Theobromine[5*]	0.82
Theophylline	1.0
Theophylline related compound F[6*]	1.09
Caffeine[*]	1.20

[*]Process impurity, included for identification only and not included in the calculation of total degradation products,
[1]N-(6-Amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)formamide,
[2]3-Methyl-1H-purine-2,6-dione,
[3]N-Methyl-5-(methylamino)-1H-imidazole-4-carboxamide hydrochloride monohydrate,
[4]1,3-Dimethyl-7,9-dihydro-1H-purine-2,6,8(3H)-trione,
[5]3,7-Dihydro-3,7-dimethylpurine-2,6(1H)-dione,
[6]7-(2-Hydroxyethyl)-1,3-dimethyl-3,7-dihydro-1H-purine-2,6-dione.

Inject reference solution (b) and (c). The test is not valid unless the resolution between the peaks due to theophylline and theophylline related compound F is not less than 2.0 in the chromatogram obtained with reference solution (c) and the relative standard deviation for replicate injections is not more than 3.0 per cent for each peak in the chromatogram obtained with reference solution (b).

Inject reference solution (b) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to theophylline related compound D is not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.2 per cent), the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent) and the sum of the areas of all the secondary peaks is not more than 2.5 times the area of the principal peak in the chromatogram with reference solution (b) (0.5 per cent). Ignore any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Assay. *For theophylline —*

Change **to**: *For theophylline* — Determine by liquid chromatography (2.4.14), as described under Related substances with the following modifications.

Test solution. Weigh and powder 20 Tablets. Disperse a quantity of the powder containing 34 mg of anhydrous Aminophylline in 160 ml of *water,* with the aid of ultrasound for 30 minutes, dilute to 200.0 ml with *water*.

Inject reference solution (a) and (c). The test is not valid unless the resolution between the peaks due to theophylline and theophylline related compound F is not less than 2.0 in the chromatogram obtained with reference solution (c) and the relative standard deviation for replicate injections is not more than 1.0 per cent in the chromatogram obtained with reference solution (a).

Inject reference solution (a) and the test solution.

Calculate the content of theophylline, $C_7H_8N_4O_2$ in the tablets.

Aminophylline Tablets. Page 1436

Identification

Change **to**: **Identification**

A. Disperse a quantity of the powdered tablets containing 0.5 g of Aminophylline with 20 ml of *water*, filter, add to the filtrate with constant stirring 1 ml of *3M hydrochloric acid*, allow to stand for a few minutes and again filter. Reserve the filtrate for test C. Wash the residue with small quantities of cold water, recrystallise from hot water and dry at 105°. On the residue, determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *theophylline IPRS* or with the reference spectrum of theophylline.

B. In the Assay of theophylline, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with reference solution (a).

C. To the filtrate obtained in Identification A, add 0.5 ml of *benzene sulphonyl chloride* and add 5 ml of *1M sodium hydroxide* to render alkaline. Shake by mechanical means for 10 minutes, add 5 ml of *3M hydrochloride acid* to acidify, chill, collect the precipitated disulphonamide to ethylenediamine and wash with water. Recrystallize the washed precipitate from water and drying at 105° for 1 hour; the dried precipitate melts at 164° to 171° (2.4.21).

Insert before **Other tests**

Related substances. Determine by liquid chromatography (2.4.14).

Test solution. Disperse a quantity of the powdered tablets containing 100 mg of anhydrous Aminophylline in 50 ml of *water*, with the aid of ultrasound for 30 minutes and dilute to 100.0 ml with *water*.

Reference solution (a). A 0.017 per cent w/v solution of *theophylline IPRS* in *water*.

Reference solution (b). A solution containing 0.0002 per cent w/v, each of, *theophylline IPRS* and *theophylline related compound D IPRS* in *water*.

Reference solution (c). Dissolve 21 mg of *theophylline IPRS* in 15 ml of *water,* with the aid of ultrasound, add 1 ml of a 0.0025 per cent w/v solution of *theophylline related compound F IPRS* in *water* and dilute to 25.0 ml with *water*.

Chromatographic system

- a stainless steel column 10 cm x 2.1 mm, packed with octadecylsilane bonded to porous silica (1.7 µm) (Such as Acquity UPLC BEH C18),
- column temperature: 40°,
- mobile phase: A. a buffer solution prepared by dissolving 770.8 mg of *ammonium acetate* in 800 ml with *water,* adjusted to pH 5.5 with *glacial acetic acid* and dilute to 1000 ml with *water,*
  B. *methanol,*
- a gradient programme using the conditions given below,
- flow rate: 0.4 ml per minute,
- spectrophotometer set at 270 nm,
- injection volume: 1 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	98	2
7	50	50
7.3	10	90

8.3	10	90
8.31	98	2
12	98	2

Name	Relative retention time
Theophylline related compound C[1*]	0.36
Theophylline related compound B[2*]	0.63
Theophylline related compound D[3]	0.69
Dimethyl uric acid[4*]	0.76
Theobromine[5*]	0.82
Theophylline	1.0
Theophylline related compound F[6*]	1.09
Caffeine[*]	1.20

[*]Process impurity, included for identification only and not included in the calculation of total degradation products,
[1]N-(6-Amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)formamide,
[2]3-Methyl-1H-purine-2,6-dione,
[3]N-Methyl-5-(methylamino)-1H-imidazole-4-carboxamide hydrochloride monohydrate,
[4]1,3-Dimethyl-7,9-dihydro-1H-purine-2,6,8(3H)-trione,
[5]3,7-Dihydro-3,7-dimethylpurine-2,6(1H)-dione,
[6]7-(2-Hydroxyethyl)-1,3-dimethyl-3,7-dihydro-1H-purine-2,6-dione.

Inject reference solution (b) and (c). The test is not valid unless the resolution between the peaks due to theophylline and theophylline related compound F is not less than 2.0 in the chromatogram obtained with reference solution (c) and the relative standard deviation for replicate injections is not more than 3.0 per cent for each peak in the chromatogram obtained with reference solution (b).

Inject reference solution (b) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to theophylline related compound D is not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.2 per cent), the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent) and the sum of the areas of all the secondary peaks is not more than 2.5 times the area of the principal peak in the chromatogram with reference solution (b) (0.5 per cent). Ignore any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Assay. *For theophylline —*
Change **to**: *For theophylline —* Determine by liquid chromatography (2.4.14), as described under Related substances with the following modifications.

Test solution. Weigh and powder 20 Tablets. Disperse a quantity of the powder containing 34 mg of anhydrous Aminophylline in 160 ml of *water,* with the aid of ultrasound for 30 minutes, dilute to 200.0 ml with *water*.

Inject reference solution (a) and (c). The test is not valid unless the resolution between the peaks due to theophylline and theophylline related compound F is not less than 2.0 in the chromatogram obtained with reference solution (c) and the relative standard deviation for replicate injections is not more than 1.0 per cent in the chromatogram obtained with reference solution (a).

Inject reference solution (a) and the test solution.

Calculate the content of theophylline, $C_7H_8N_4O_2$ in the tablets.

Amlodipine and Nebivolol Tablets. Page 1453

Dissolution. Medium
Change **to**: Medium. 900 ml of *0.01 M hydrochloric acid*.

Amlodipine and Olmesartan Medoxomil Tablets. Page 5128

Related substances. *Reference solution (b),* line 1
Change **from**: 0.8 per cent
to: 0.4 per cent

Reference solution (c), line 2
Change **from**: 1.0 ml of reference solution (b)
to: 2.0 ml of reference solution (b)

Amorolfine Hydrochloride. Page 1461

Identification

Change **to**: A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *amorolfine hydrochloride IPRS* or with the reference spectrum of amorolfine hydrochloride.

B. A 0.5 per cent w/v solution gives the reaction (A) of chloride (2.3.1).

Related substances

Change **to**: **Related substances**. Determine by liquid chromatography (2.4.14).

Buffer solution. Dissolve 3.5 g of *dipotassium hydrogen phosphate* in 1000 ml of *water*, adjusted to pH 7.0 with *orthophosphoric acid*.

Test solution. Dissolve 20 mg of the substance under examination in mobile phase A and dilute to 20.0 ml with mobile phase A.

Reference solution (a). A 0.0001 per cent w/v solution of *amorolfine hydrochloride IPRS* in mobile phase A.

Reference solution (b). Dissolve 4 mg of *amorolfine for system suitability IPRS* (containing impurities D, E, I and J) in mobile phase A and dilute to 5.0 ml with mobile phase A.

Reference solution (c). Dissolve 4 mg of *amorolfine for peak identification IPRS* (containing amorolfine impurity M) in mobile phase A and dilute to 5.0 ml with mobile phase A.

Chromatographic system

- a stainless steel column 15 cm x 4.6 mm, packed with end capped amidohexadecylsilane bonded to porous silica (3 µm),
- mobile phase: A. a mixture of 35 volumes of the buffer solution, 60 volumes of *methanol* and 5 volumes of *acetonitrile*,
  B. a mixture of 10 volumes of the buffer solution, 60 volumes of *methanol* and 30 volumes of *acetonitrile*,
- a gradient programme using the conditions given below,
- flow rate: 1.5 ml per minute,
- spectrophotometer set at 214 nm,
- injection volume: 20 µl.

Time (in min)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	90	10
2	90	10
25	0	100
25.1	90	10
30	90	10

Name	Relative retention time
Amorolfine impurity M[1] (peak 1)	0.56
Amorolfine impurity M[1] (peak 2)	0.60
Amorolfine impurity D[2]	0.85
Amorolfine impurity J[3]	0.97
Amorolfine (Retention time: about 15 minutes)	1.0
Amorolfine impurity I[4]	1.05
Amorolfine impurity E[5] (peak 1)	1.14
Amorolfine impurity E[5] (peak 2)	1.17

[1]mixture of (1*RS*,2*RS*)-3-[(2*RS*,6*SR*)-2,6dimethylmorpholin-4-yl]-2-methyl-I-[4-(2-methylbutan-2-yl) phenyl]propan-1-ol and (1*RS*,2*SR*)-3-[(2*RS*,6*SR*)-2,6-dimethylmorpholin-4-yl]-2-methyl-1-[4-(2-methylbutan-2yl)phenyl]propan-1-ol,
[2](2*RS*,6*SR*)-2,6-dimethyl-4-[(2*RS*)-3-(4-tert-butylphenyl)-2-methylpropyl]morpholine,
[3](2*RS*,6*SR*)-2,6-dimethyl-4-[(2*RS*)-2-methyl-3-[3-(2-methylbutan-2-yl)phenyl]propyl]morpholine,
[4](2*RS*,6*SR*)-2,6-dimethyl-4-[(2*RS*)-2-methyl-3-[4-[(2*E*)-3-methylbutan-2-yl]phenyl]propyl]morpholine,
[5]mixture of (2*RS*,6*RS*]-2,6-dimethyl-4-[(2*R*)-2-methyl-3-[4-(2-methylbulan-2-yl)phenyl]propyl]morpholine and (2*RS*,6*RS*) -2,6-dimethyl-4-[(2*S*]-2-methyl-3-[4-(2-methylbutan- 2-yl)phenyl]propyl]morpholine.

Inject reference solution (b) to identify the peaks due to amorolfine impurity D, E, I and J.

Inject reference solution (c) to identify the peaks due to amorolfine impurity M (peak 1 and 2).

Inject reference solution (a) and (b). The test is not valid unless the resolution between the peaks due to amorolfine impurity J and amorolfine is not less than 2.0 in the chromatogram obtained with reference solution (b) and the signal-to-noise ratio is not less than 20 in the chromatogram obtained with reference solution (a).

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to amorolfine impurity D is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent), the sum of the areas of two peaks corresponding to amorolfine impurity E is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent), the area of any peak corresponding to amorolfine impurity I is not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent), the area of the two peaks corresponding to amorolfine impurity M (peak 1 and peak 2), each of, is not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent), the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent) and the sum of areas of all the secondary peaks is not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.4 per cent). Ignore any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Sulphated ash
Change **from**: Not more than 0.5 per cent.
to: Not more than 0.1 per cent.

Amoxycillin Sodium. Page1464

Assay. *Test solution*, line 1 and 2
Change **from**: Dissolve a quantity containing 120 mg of Amoxycillin in the solvent mixture...
to: Dissolve 125 mg of the substance under examination in the solvent mixture…

Amoxycillin and Potassium Clavulanate Injection. Page 1469

Usual strengths
Change **to**: **Usual strengths**. Amoxycillin 1000 mg and Clavulanic acid 200 mg per vial; Amoxycillin 500 mg and Clavulanic acid 100 mg per vial; Amoxycillin 250 mg and Clavulanic acid 50 mg per vial.

Assay. *Reference solution*
Change **to**: *Reference solution*. A solution of *amoxycillin trihydrate IPRS* containing 0.06 per cent w/v of amoxycillin and *lithium clavulanate IPRS* containing 0.012 per cent w/v of clavulanic acid in *water*.

Amoxycillin and Potassium Clavulanate Oral Suspension. Page 1470

Assay. *Reference solution*
Change **to**: *Reference solution*. A solution of *amoxycillin trihydrate IPRS* containing 0.05 per cent w/v of amoxycillin and *lithium clavulanate IPRS* containing 0.00712 per cent w/v of clavulanic acid in *water*.

Amoxycillin and Potassium Clavulanate Tablets. Page 1471

Usual strength
Change **to**: **Usual strengths**. Amoxycillin 875 mg and Clavulanic acid 125 mg; Amoxycillin 500 mg and Clavulanic acid 125 mg; Amoxycillin 250 mg and Clavulanic acid 125 mg.

Identification. Line 3 and 4
Change **from**: the reference solution.
to: reference solution (c).

Dissolution. Change **to**:

Dissolution (2.5.2). *(Tablets labelled for veterinary use only are exempt from this requirement).*

Apparatus No. 2 (Paddle),
Medium. 900 ml of *water*,
Speed and time. 75 rpm and 30 minutes or 45 minutes where the Tablets are labelled as chewable.

Withdraw a suitable volume of the medium and filter.

Determine by liquid chromatography (2.4.14).

Test solution. Use the filtrate, dilute, if necessary, with the dissolution medium.

Reference solution (a). Dissolve 110.8 mg of *amoxycillin trihydrate IPRS* in *water* with the aid of magnetic stirrer and dilute to 50.0 ml with *water*.

Reference solution (b). Dissolve 35.6 mg of *lithium clavulanate IPRS* in *water* with the aid of magnetic stirrer and dilute to 50.0 ml with *water*.

Reference solution (c). Dilute a suitable volume of reference solution (a) and reference solution (b) with *water* to obtain a solution having similar concentration to that of the test solution.

Use the chromatographic system as described under Assay.

Inject reference solution (c) and the test solution.

Calculate the content of $C_{16}H_{19}N_3O_5S$ and $C_8H_9NO_5$ in the medium.

Q. Not less than 85 per cent of the stated amount of $C_{16}H_{19}N_3O_5S$ and not less than 80 per cent of the stated amount of $C_8H_9NO_5$.

For tablets labelled as chewable. Not less than 80 per cent of the stated amount of the $C_{16}H_{19}N_3O_5S$ and $C_8H_9NO_5$ is dissolved in 45 minutes.

Assay. *Reference solution*
Change **to**: *Reference solution (a)*. Dissolve *amoxycillin trihydrate IPRS* equivalent to 50 mg of amoxycillin in *water* with the aid of magnetic stirrer and dilute to 100.0 ml with *water*.

Reference solution (b). Dissolve *lithium clavulanate IPRS* equivalent to 31.25 mg of clavulanic acid in *water* with the aid of magnetic stirrer and dilute to 25.0 ml with *water*.

Reference solution (c). Dilute a suitable volume of reference solution (a) and reference solution (b) with *water* to obtain a solution having similar concentration to that of the test solution.

After chromatographic system, lines 1 to 9
Change **to**: The relative retention time with reference to amoxycillin for clavulanic acid is about 0.5.

Inject reference solution (c). The test is not valid unless the resolution between amoxycillin and clavulanic acid peak is not less than 3.5, the column efficiency is not less than 550 theoretical plates, the tailing factor is not more than 1.5 and the relative standard deviation for replicate injections is not more than 2.0 per cent for each component.

Inject reference solution (c) and the test solution.

Amphotericin B. Page 1472
Identification. B, line 7
Change **from**: 0.5 to 0.6;
to: 0.57 to 0.61;

Line 9
Change **from**: about 0.9
to: 0.87 to 0.93

Tetraenes. Lines 1 and 2
Change **from**: **Tetraenes**. Not more than 15.0 per cent (for parenteral use, not more than 10.0 per cent),
to: **Limit of amphotericin A (Tetraenes)**. Not more than 15 per cent (for parenteral use, not more than 5 per cent),

Anastrozole Tablets. Page 1485
Dissolution. Chromatographic system, line 2
Change **from**: octadecylsilane
to: octylsilane and octadecylsilane
Line 3
Change **from**: Hichrom RPB C18

to: Hichrom RPB C8/C18

Aprepitant. Page 1493

Insert before **Water**

Heavy metals (2.3.13). 1.0 g complies with the limit test for heavy metals, Method B (20 ppm).

Sulphated ash (2.3.18). Not more than 0.1 per cent.

Aripiprazole. Page 1501

Sulphated ash. Line 1

Change **from**: Not more than 0.2 per cent

to: Not more than 0.1 per cent

Aripiprazole Tablets. Page 1502

Dissolution. Last para

Change **to**: Q. Not less than 75 per cent of the stated amount of $C_{23}H_{27}Cl_2N_3O_2$.

Atenolol. Page 5131

Related substances. *Buffer solution*, line 2 and 3

Change **from**: *water*, adjusted to pH 3.0 with *orthophosphoric acid*.

to: *water*.

Chromatographic system, line 8

Change **from**: the buffer solution,

to: the buffer solution. Adjust to pH 3.0 with *orthophosphoric acid*.

Atracurium Besylate. Page 1540

Related substances. Last para, lines 23 to 26

Change **from**: Ignore any peak with an area less than 0.05 times the sum of the areas of three principal peaks in the chromatogram obtained with reference solution (b) (0.05 per cent).

to: Ignore any peak due to benzene sulphonic acid and any peak with an area less than 0.05 times the sum of the areas of three principal peaks in the chromatogram obtained with reference solution (b) (0.05 per cent).

Atorvastatin Tablets. Page 1536

Dissolution. Last para, line 1

Change **from**: 70 per cent

to: 80 per cent

Related substances. Change **to**:

Related substances. Determine by liquid chromatography (2.4.14).

Buffer solution A. A mixture of 92.5 volumes of *acetonitrile* and 7.5 volumes of *tetrahydrofuran* (stabilizer-free).

Buffer solution B. A 0.575 per cent w/v solution of*monobasic ammonium phosphate* in *water*, adjusted to pH 4.3 with 10 per cent v/v of *acetic acid* or *ammonia solution*

Test solution. Transfer a quantity of the powdered tablets containing 50 mg of atorvastatin to a 50-m1 volumetric flask, add 30 ml of *N,N-dimethylformamide,* shake mechanically for 15 minutes, and dilute to volume with *N,N-dimethylformamide* and filter.

Reference solution (a). A solution of *atorvastatin calcium IPRS* in *N,N-dimethylformamide*containing 0.0005 per cent of atorvastatin.

*Reference solution (b).*A solution containing 0.006 per cent w/v of *atorvastatin calcium IPRS,* 0.005 per cent w/v of *atorvastatin impurity B IPRS*, 0.001 per cent w/v of *atorvastatin impurity H IPRS* and 0.00005 per cent w/v of*atorvastatinimpurity D IPRS*in*N,N-dimethylformamide.*

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm),
- sample temperature: 10°,
- mobile phase: A. a mixture of 58 volumes of buffer solution B and 42 volumes of buffer solution A,
  B. a mixture of 20 volumes of buffer solution B, 20 volumes of buffer solution A and 60 volumes of *methanol,*
- a gradient programme using the conditions given below,
- spectrophotometer set at 244 nm,
- injection volume: 20 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)	Flow rate (ml per min.)
0	100	0	1.8
30	100	0	1.8
45	25	75	1.5
50	25	75	1.5
55	20	80	1.5
58	100	0	1.8
65	100	0	1.8

[NOTE- For reference solution (a) run time is 30 minutes, for reference solution (b) and the test solution, the run time is 65 minutes]

Name	Relative retention time	Correction factor
Atorvastatin amide[1*]	0.44	--
Atorvastatin impurity A[2*]	0.84	--
Atorvastatin pyrrolidone analog[3]	0.88	1.47
Atorvastatin impurity B[4*]	0.94	--
Atorvastatin	1.00	--
Atorvastatin impurity C[5*]	1.09	--
Atorvastatin pyrrolidone lactone[6*]	1.62	--
Atorvastatin impurity H[7]	1.00	0.85
Atorvastatin epoxy pyrrolooxazin 6-hydroxy analog[8]	1.06	1.89
Atorvastatin methyl ester[9*]	1.12	--
Atorvastatin epoxy pyrrolooxazin 7-hydroxy analog, if present[10]	1.14	1.89
Atorvastatin epoxy THF analog[11+]	1.20	0.89
Atorvastatin impurity D[12]	1.27	0.89
Atorvastatin tert-butyl ester[13*]	1.49	--

[NOTE- The relative retention times of all peaks eluting before atorvastatin impurity H are calculated with respect to the atorvastatin peak. The relative retention times for all peaks eluting after atorvastatin impurity H are calculated with respect to atorvastatin impurity H]

[*] Process impurity included in the table for identification only. Process impurities are controlled in the drug substance, and are not to be reported or included in the total impurities for the drug product.

[+]Atorvastatin impurity D can undergo transformation equilibrium to the atorvastatin epoxy THF analog. The equilibrium can be shifted under slightly acidic conditions and therefore some products could have a combined specification reported under atorvastatin impurity D.

[1](3R,5R)-7-{(3R,5R)-7-[2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1H-pyrrol-1-yl]-3,5-dihydroxyheptanamido}-3,5-dihydroxyheptanoic acid.

[2](3R,5R)-7-[2-Isopropyl-4,5-diphenyl-3-(phenylcarbamoyl)-1H-pyrrol-1-yl]-3,5-dihydroxyheptanoic acid.

[3](3R,5R)-7-[5-(4-Fluorophenyl)-3-isopropyl-2-oxo-4-phenyl-3-(phenylcarbamoyl)-2,3-dihydro-1H-pyrrol-1-yl]-3,5-dihydroxyheptanoic acid.

[4](3S,5R)-7-[2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1H-pyrrol-1-yl]-3,5-dihydroxyheptanoic acid.

[5](3R,5R)-7-[2,3-Bis(4-fluorophenyl)-5-isopropyl-4-(phenylcarbamoyl)-1H-pyrrol-1-yl]-3,5-dihydroxyheptanoic acid.

[6]5-(4-Fluorophenyl)-1-{2-[(2R,4R)-4-hydroxy-6-oxotetrahydro-2H-pyran-2-yl]ethyl}-3-isopropyl-2-oxo-N,4-diphenyl-2,3-dihydro-1H-pyrrole-3-carboxamide.

[7]5-(4-Fluorophenyl)-1-{2-[(2R,4R)-4-hydroxy-6-oxotetrahydro-2H-pyran-2-yl]ethyl}-2-isopropyl-N,4-diphenyl-1H-pyrrole-3-carboxamide.

[8]4-{6-(4-Fluorophenyl)-7,8-epoxy-6-hydroxy-8a-isopropyl-7-phenyl-8-(phenylcarbamoyl)hexahydro-2H-pyrrolo[2,1-b][1,3]oxazin-2-yl}-3-hydroxybutanoic acid.

[9](3R,5R)-Methyl7-(2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1H-pyrrol-1-yl)-3,5-dihydroxyheptanoate.

[10](3R)-4-(1b-(4-Fluorophenyl)-7-hydroxy-7-isopropyl-1a-phenyl-7a-(phenylcarbamoyl)hexahydro-1aH-oxireno[2′,3′:3,4]pyrrolo[2,1-b][1,3]oxazin-3-yl)-3-hydroxybutanoic acid.

[11]4-(4-Fluorophenyl)-2,4-dihydroxy-2-isopropyl-N,5-diphenyl-3,6-dioxabicyclo[3.1.0]hexane-1-carboxamide.

[12]3-(4-Fluorobenzoyl)-2-isobutyryl-N,3-diphenyloxirane-2-carboxamide.

[13](3R,5R)-tert-Butyl7-(2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1H-pyrrol-1-yl)-3,5-dihydroxyheptanoate.

Inject reference solution (b). The test is not valid unless the resolution between the peaks due to atorvastatin impurity B and atorvastatinis not less than 1.4, the tailing factor is not more than 2.0 for the atorvastatin peak and the relative standard deviation for replicate injections is not more than 5 per cent for the atorvastatin peak and the signal-to-noise ratio is not less than 10.0 for atorvastatin impurity D.

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to atorvastatin pyrrolidone analog, atorvastatin epoxy pyrrolooxazin 6-hydroxy analog, and atorvastatin impurity D, each of, is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent), the area of any peak corresponding to atorvastatin impurity H, atorvastatin epoxy pyrrolooxazin 7-hydroxy analog and atorvastatin epoxy THF analog, each of, is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent), the area of any other secondary peak is not more than 0.4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent) and the sum of the areas of all the secondary peaks is not more than 8 times the area of the principal peak in the chromatogram obtained with reference solution (a) (4.0 per cent).

Atropine Sulphate. Page 1545

Apoatropine. Delete the requirement.
Foreign alkaloids and decomposition products. Delete the requirement.

Water. Line 1
Change **from**: Not more than 4.0 per cent,
to: 2.0 per cent to 4.0 per cent,

Related substances

Change **to**: **Related substances**. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve 24 mg of the substance under examination in mobile phase A and dilute to 100.0 ml with mobile phase A.

Reference solution (a). A 0.0024 per cent w/v solution of *atropine sulphate IPRS* in mobile phase A. Dilute 1.0 ml of the solution to 100.0 ml with mobile phase A.

Reference solution (b). Dissolve 5 mg of *atropine impurity B IPRS* in test solution and dilute to 20.0 ml with test solution. Dilute 5.0 ml of the solution to 25.0 ml with mobile phase A.

*Reference solution (c).*Dissolve the contents of a vial of *atropine for peak identification IPRS* (containing atropine impurities A, D, E, F, G and H) in 1.0 ml of mobile phase A.

*Reference solution (d).*A 0.00005 per cent w/v solution of *atropine impurity C IPRS* (*tropic acid*) in mobile phase A.

Chromatographic system
- a stainless steel column 10 cm x 4.6 mm, packed with end-capped octadecylsilane bonded to porous silica (3 µm),
- mobile phase: A. a 0.38 per cent w/v solution of *sodium lauryl sulphate* in a mixture of 65.5 volumes of a buffer solution prepared by dissolving 7 g of *potassium dihydrogen phosphate* in 1000 ml of *water*, adjusted to pH 3.3 with *0.05 M orthophosphoric acid* and mix with 34.5 volumes of *acetonitrile*,
  B. *acetonitrile*,
- a gradient programme using the conditions given below,
- flow rate: 1 ml per minute,
- spectrophotometer set at 210 nm,
- injection volume: 10 µl.

Time (in min)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)

0	95	5
2	95	5
20	70	30
22	95	5
25	95	5

Name	Relative retention time	Correction factor
Atropine impurity C[1]	0.2	0.6
Atropine impurity E[2]	0.67	---
Atropine impurity D[3]	0.73	---
Atropine impurity F[4]	0.80	---
Atropine impurity B[5]	0.89	---
Atropine impurity H*	0.93	---
Atropine (Retention time: about 11 minutes)	1.0	---
Atropine impurity G[6]	1.1	---
Atropine impurity A[7]	1.7	0.6

*Unknown structure
[1](2*RS*)-3-hydroxy-2-phenylpropanoic acid (tropic acid),
[2](1*S*,3*R*,5*S*,6*RS*)-6-hydroxy-8-methyl-8-azabicyclo[3.2.1]oct-3-yl (2*S*)-3-hydroxy-2-phenylpropanoate(7-hydroxyhyoscyamine),
[3](1*R*,3S,5R,6*RS*)-6-hydroxy-8-methyl-8-azabicyclo[3.2.1]oct-3-yl (2*S*)-3-hydroxy-2-phenylpropanoate(6-hydroxyhyoscyamine),
[4](1*R*,2*R*,4*S*,5*S*,7*s*)-9-methyl-3-oxa-9-azatricyclo[3.3.I.O^{2,4}]non-7-yl (2*S*)-3-hydroxy-2-phenylpropanoate (hyoscine),
[5](1*R*,3*r*,5*S*)-8-azabicyclo[3.2.1]oct-3-yl (2*RS*)-3-hydroxy-2-phenylpropanoate(noratroplne),
[6](1*R*,3*r*,5*S*)-8-methyl-8-azabicyclo[3.2.1] oct-3-yl *(2RS)*-2-hydroxy-3-phenylpropanoate (littorine),
[7](1*R*,*3r*,5*S*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl2-phenylpropenoate (apoatropine).

Inject reference solution (c) to identify the peaks due to atropine impurity A, D, E, F, G and H.

Inject reference solution (d) to identify the peak due to atropine impurity C.

Inject reference solution (b). The test is not valid unless the resolution between the peaks due to atropine impurity B and atropine is not less than 2.5.

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to atropine impurity E and atropine impurity H, each of, is not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent), the area of any secondary peak corresponding to atropine impurity A, B, C, D, F and G, each of, is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent), the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent) and the sum of areas of all the secondary peaks is not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent). Ignore any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Bacitracin Zinc. Page 1571

Pyrogens

Change **from**: **Pyrogens** (2.2.8). If intended for administration by spraying into internal body cavities without a further appropriate procedure for the removal of pyrogens, it complies with the test for pyrogens. Inject per kilogram of the rabbit's mass 1 ml of the supernatant liquid obtained by centrifuging a suspension containing 11 mg per milliliter in a 0.9 per cent solution of*sodium chloride.*

to: *Bacitracin Zinc intended for administration as a spray in internal body cavities without a further appropriate procedure for the removal of pyrogen complies with the following additional requirement.*

Pyrogens (2.2.8). Complies with the test for pyrogens, using per kg of the rabbit's weight, 1 ml of the supernatant liquid obtained by centrifuging a suspension containing 11 mg per ml in a 0.9 per cent w/v solution of*sodium chloride.*

Betahistine Tablets. Page 1614

Assay. Chromatographic system

Change **to**: Use chromatographic system as described under Related substances with the following modification.
– column temperature: 50º,

Betamethasone Valerate Cream. Page 1629

Identification. B

Change **to**: B. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with reference solution (c).

Insert before **Other tests**

Related substances. Determine by liquid chromatography (2.4.14).

Solvent mixture A. Equal volumes of *tetrahydrofuran* and *water*.

Solvent mixture B. 40 volumes of *acetonitrile* and 60 volumes of *water*.

Test solution. Transfer a quantity of the cream containing 1 mg of betamethasone to a suitable glass centrifuge tube, add 15 ml of solvent mixture A and mix with a vortex mixture to disperse the sample thoroughly. Add 35.0 ml of solvent mixture B, sonicate for 10 minutes with intermittent shaking and centrifuge to obtain a clear supernatant. Pass through a suitable filter of 0.2 µm pore size using a glass syringe.

Reference solution (a). A solution containing 0.0025 per cent w/v, each of, *betamethasone IPRS, betamethasone valerate IPRS* and *betamethasone valerate related compound A IPRS* in solvent mixture B. Dilute 1.0 ml of the solution to 100.0 ml with solvent mixture B.

Reference solution (b). A solution containing 0.0025 per cent w/v of *betamethasone valerate IPRS* and 0.001 per cent w/v of *betamethasone valerate related compound A IPRS* in solvent mixture B.

Reference solution (c). A 0.0025 per cent w/v solution of *betamethasone valerate IPRS* in solvent mixture B.

Chromatographic system

- a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (3.5 µm),
- sample temperature: 4°,
- mobile phase: A. *water*,
  B. *acetonitrile,*
- a gradient programme using the conditions given below,
- flow rate: 1 ml per minute,
- spectrophotometer set at 240 nm,
- injection volume: 100 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	63	37
7	63	37
15	30	70
19	30	70
19.1	10	90
21	10	90
21.1	63	37
25	63	37

Name	Relative retention time
Betamethasone	0.30
Betamethasone Valerate	1.0
Betamethasone valerate related compound A[1]	1.04

[1]9-Fluoro-11β, 17-dihydroxy-16β-methyl-3, 20-dioxopregna-1,4-dien-21-yl valerate.

Inject reference solution (a) and (b). The test is not valid unless the resolution between the peak due to betamethasone valerate and betamethasone valerate related compound A is not less than 2.0 in the chromatogram obtained with reference solution (b) and the relative standard deviation for replicate injections is not more than 5 per cent in the chromatogram obtained with reference solution (a).

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to betamethasone and betamethasone valerate related compound A, each of is not more than 0.8 times the area of the corresponding peak in the chromatogram obtained with reference solution (a) (1.0 per cent), the area of any other secondary peak is not more than 0.8 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent) and the sum of areas of all the secondary peaks is not more than 1.6 times the area of the principal peak in the chromatogram obtained with reference solution (a) (2.0 per cent). Ignore any peak with an area less than 0.08 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent).

Assay

Change **to**: **Assay**. Determine by liquid chromatography (2.4.14), as described under Related substances with the following modifications.

Inject reference solution (b) and (c). The test is not valid unless the resolution between the peaks due betamethasone valerate and betamethasone valerate related compound A is not less than 2.0 in the chromatogram obtained with reference solution (b), the tailing factor is not more than 2.0 and the relative standard deviation for replicate injections is not more than 1.0 per cent in the chromatogram obtained with reference solution (c).

Inject reference solution (c) and the test solution.

Calculate the content of $C_{22}H_{29}FO_5$ in the cream.

Betamethasone Valerate Ointment. Page 1630

Identification. B

Change **to**: B. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with reference solution (c).

Insert before **Other tests**

Related substances. Determine by liquid chromatography (2.4.14).

Solvent mixture A. Equal volumes of *tetrahydrofuran* and *water*.

Solvent mixture B. 40 volumes of *acetonitrile* and 60 volumes of *water*.

Test solution. Transfer a quantity of the Ointment containing 1 mg of betamethasone to a suitable glass centrifuge tube, add 15 ml of solvent mixture A and mix with a vortex mixture to disperse the sample thoroughly. Add 35.0 ml of solvent mixture B, sonicate for 10 minutes with intermittent shaking and centrifuge to obtain a clear supernatant. Use the clear supernatant.

Reference solution (a). A solution containing 0.0025 per cent w/v, each of, *betamethasone IPRS, betamethasone valerate IPRS* and *betamethasone valerate related compound A IPRS* in solvent mixture B. Dilute 1.0 ml of the solution to 100.0 ml with solvent mixture B.

Reference solution (b). A solution containing 0.0025 per cent w/v of *betamethasone valerate IPRS* and 0.001 per cent w/v of *betamethasone valerate related compound A IPRS* in solvent mixture B.

Reference solution (c). A 0.0025 per cent w/v solution of *betamethasone valerate IPRS* in solvent mixture B.

Chromatographic system

- a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (3.5 µm),
- sample temperature: 4°,
- mobile phase: A. *water*,
  B. *acetonitrile,*
- a gradient programme using the conditions given below,
- flow rate: 1 ml per minute,
- spectrophotometer set at 240 nm,
- injection volume: 100 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	63	37
7	63	37
15	30	70
19	30	70
19.1	10	90
21	10	90
21.1	63	37
25	63	37

Name	Relative retention time
Betamethasone	0.30
Betamethasone valerate	1.0
Betamethasone valerate related compound A[1]	1.04

[1]9-Fluoro-11β, 17-dihydroxy-16β-methyl-3, 20-dioxopregna-1,4-dien-21-yl valerate.

Inject reference solution (a) and (b). The test is not valid unless the resolution between the peak due to betamethasone valerate and betamethasone valerate related compound A is not less than 2.0 in the chromatogram obtained with reference solution (b) and the relative standard deviation for replicate injections is not more than 5 per cent in the chromatogram obtained with reference solution (a).

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to betamethasone and betamethasone valerate related compound A, each of is not more than 0.8 times the area of the corresponding peak in the chromatogram obtained with reference solution (a) (1.0 per cent), the area of any other secondary peak is not more than 0.8 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent) and the sum of areas of all the secondary peaks is not more than 1.6 times the area of the principal peak in the chromatogram obtained with reference solution (a) (2.0 per cent). Ignore any peak with an area less than 0.08 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent).

Assay
Change **to**: **Assay**. Determine by liquid chromatography (2.4.14), as described under Related substances with the following modifications.

Inject reference solution (b) and (c). The test is not valid unless the resolution between the peaks due betamethasone valerate and betamethasone valerate related compound A is not less than 2.0 in the chromatogram obtained with reference solution (b), the tailing factor is not more than 2.0 and the relative standard deviation for replicate injections is not more than 1.0 per cent in the chromatogram obtained with reference solution (c).

Inject reference solution (c) and the test solution.

Calculate the content of $C_{22}H_{29}FO_5$ in the ointment.

Bisacodyl Gastro-resistant Tablets. Page 1644

Assay. *Test solution*
Change **to**: *Test solution*. Weigh and powder 20 tablets. Disperse a quantity of powder containing 50 mg of Bisacodyl in 70 ml of the solvent mixture, with the aid of ultrasound for 20 minutes with intermittent shaking and dilute to 100.0 ml with the solvent mixture. Dilute 5.0 ml of the solution to 50.0 ml with the solvent mixture.

Related substances
Insert before *Solvent mixture*
NOTE — Use freshly prepared solutions.

Budesonide. Page 1674

Related substances. Change **to**:
Related substances. Determine by liquid chromatography (2.4.14).

Solvent mixture. 30 volumes of*acetonitrile*and70 volumes of *water.*

Test solution. Dissolve 60 mg of the substance under examination in 30 ml of *acetonitrile* and dilute to 100.0 ml with *water.*

Reference solution (a). Dissolve 60 mg of *budesonide IPRS* in 30 ml of *acetonitrile* and dilute to 100.0 ml with *water.*

Reference solution (b). Dilute 1.0 ml of reference solution (a) to 100.0 ml with the solvent mixture. Further dilute 1.0 ml of the solution to 10.0 ml with the solvent mixture.

Reference solution (c). A solution containing 0.03 per cent w/v, each of, *budesonide impurity E IPRS, budesonide impurity G IPRS* and *budesonide impurity L IPRS* in *acetonitrile*.

Reference solution (d). Dilute 0.5 ml of reference solution (c) to 50.0 ml with reference solution (a).

Reference solution (e). Dilute 1.0 ml of reference solution (b) to 20.0 ml with the solvent mixture.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (3 µm),
- column temperature: 50°*[Note—The resolution between budesonide related compound E and budesonide related compound L may be improved by lowering the temperature, but to not less than 40°],*

- sample temperature: 4°,
- mobile phase: A. a 0.05 per cent v/v of *glacial acetic acid* in *water,* adjusted to pH 3.9 with *potassium hydroxide,*
  B. *acetonitrile*,
- a gradient programme using the conditions given below,
- flow rate: 1.5ml per minute,
- spectrophotometer set at 240 nm,
- injection volume: 50 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	75	25
5	75	25
35	68	32
42	59	41
59	25	75
60	75	25
70	75	25

Name	Relative retention time
16α-Hydroxyprednisolone[1]	0.12
Budesonide acetaldehyde acetal (epimers)[2#]	0.39, 0.40
Budesonide d-homo analog[3]*	0.47
Desonide[4] *	0.51
Budesonide glyoxal (epimers)[5#]	0.76, 0.78
Budesonide impurity E[6]	0.86
Budesonide impurity L[7]	0.88
Budesonide epimer B	0.96
Budesonide epimer A	1.00
Budesonide impurity G (epimers)[8#]	1.07, 1.08
Budesonide 21-acetate (epimers)[9#]	1.39, 1.40
Budesonide 21-butyrate[10]	1.48

#Limit includes both epimers
* This impurity is to be reported under total unspecified impurities. Do not report it under total specified impurities.
[1]11β,16α,17,21-Tetrahydroxypregna-1,4-diene-3,20-dione.
[2]16α,17-[Ethylidenebis(oxy)]-11β,21-dihydroxypregna-1,4-diene-3,20-dione.
[3]16α,17-[Butylidenebis(oxy)]-11β-hydroxy-17-(hydroxymethyl)-d-homoandrosta-1,4-diene-3,17a-dione; also known as d-homobudesonide.
[4]16α,17-[1-Methylethylidenebis(oxy)]-11β, 21-dihydroxypregna-1,4-diene-3,20-dione.
[5]16α,17-[Butylidenebis(oxy)]-11β-hydroxy-3,20-dioxopregna-1,4-dien-21-al; also known as 21-dehydrobudesonide.
[6]Also known as 14,15-dehydrobudesonide or budesonide 14-ene.
[7]Also known as 11-ketobudesonide.
[8]Also known as 1,2-dihydrobudesonide.
[9]16α,17-[Butylidenebis(oxy)]-11β-hydroxypregna-1,4-diene-3,20-dione-21-yl acetate.
[10]16α,17-[Butylidenebis(oxy)]-11β,21-dihydroxypregna-1,4-diene-3,20-dione-21-butyrate.

Inject reference solution (b), (d) and (e). The test is not valid unless the resolution between the peaks due to budesonide impurity E and budesonide impurity L is not less than 1.2 and between budesonide epimer A and the first epimer of budesonide impurity G is not less than 3.0 in the chromatogram obtained with reference solution (d),the tailing factor is not more than 1.5 for budesonide epimer B, the relative standard deviation for the sum of peak areas of the two budesonide epimer is not more than 5.0 per cent in the chromatogram obtained with reference solution (b) and the signal-to-noise ratio of the principal peak is not less than 10 in the chromatogram obtained with reference solution (e).

Inject reference solution (b) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to 16 α-hydroxyprednisolone and budesonide impurity L, each of, is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent), the area of any peak corresponding to budesonide acetaldehyde acetal (epimers), budesonide d-homo analog, desonide, budesonide glyoxal (epimers), budesonide impurity E, budesonide impurity G (epimers) and budesonide 21-acetate (epimers), each of, is not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent), the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent) and the sum of the areas of all the specified secondary peaks is not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.4 per cent), and the sum of the areas of all the unspecified

secondary peaks is not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.4 per cent). Ignore any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent) and the peaks eluting after 60 minutes.

Bosutinib. Page 1657

Line 1

Change **from**: $C_{26}H_{29}Cl_2N_5O_3$ Mol. Wt. 530.5 (anhydrous form)

to:

$C_{26}H_{29}Cl_2N_5O_3$	Mol. Wt. 530.5 (anhydrous)
$C_{26}H_{29}Cl_2N_5O_3$. H_2O	Mol. Wt. 548.5 (monohydrate)
$C_{26}H_{29}Cl_2N_5O_3$. $2H_2O$	Mol. Wt. 566.5 (dihydrate)

Water

Change **from**: Not more than 5.0 per cent, determined on0.5 g.

to: Not more than 1.0 per cent for anhydrous form, determined on 1.0 g; 3.0 per cent to 5.0 per cent for monohydrate form and 6.0 per cent to 9.0 per cent for dihydrate form, determined on 0.5 g.

Aqueous Calamine Cream. Page 1715

Assay. Change **to**:

Assay. Weigh 0.5 g in a porcelain dish, heat gently over a small flame until the base is completely volatilised or charred. Increase the heat until all the carbon is removed. Dissolve the residue in 10 ml of *2 M acetic acid* and add sufficient *water* to produce 50 ml. To the resulting solution, add about 50 mg of *xylenol orange triturate* and sufficient *hexamine* to produce violet-pink colour. Add a further 2 g of *hexamine* and titrate with *0.05 M disodium edetate* until the solution becomes yellow.

1 ml of *0.05 M disodium edetate* is equivalent to 0.00407 g of ZnO.

Calamine Ointment. Page 1716

Assay. Change **to**:

Assay. Weigh 0.5 g in a porcelain dish, heat gently over a small flame until the base is completely volatilised or charred. Increase the heat until all the carbon is removed. Dissolve the residue in 10 ml of *2 M acetic acid*and add sufficient *water*to produce 50 ml. To the resulting solution, add about 50 mg of *xylenol orange triturate*and sufficient *hexamine*to produce violet-pink colour. Add a further 2 g of *hexamine* and titrate with *0.05 M disodium edetate*until the solution becomes yellow.

1 ml of *0.05 M disodium edetate* is equivalent to 0.00407 g of ZnO.

Capreomycin Injection. Page 1726

Capreomycin 1 content. *Reference solution*

Change **from**: A 0.025 per cent w/v solution of *capreomycin sulphate IPRS* in *water*.

to: A solution of *capreomycin sulphate IPRS* containing 0.025 per cent w/v of capreomycin in *water*.

Carbamazepine. Page 1730

Para 2

Change **to**: Carbamazepine contains not less than 98.0 per cent and not more than 102.0 per cent of $C_{15}H_{12}N_2O$, calculated on the dried basis.

Identification. B

Change **to**: B. In the Assay, the principal peak in the chromatogram obtained with test solution (b) corresponds to the peak in the chromatogram obtained with reference solution (a).

Related substances. Change **to**:

Related substances. Determine by liquid chromatography (2.4.14).

Solvent mixture. Equal volumes of *methanol* and *water.*

Test solution (a). Dissolve 100 mg of the substance under examination in 50 ml of *methanol* and dilute to 100.0 ml with *water*.

Test solution (b). Dilute 1.0 ml of test solution (a) to 10.0 ml with the solvent mixture.

Reference solution (a). Dissolve 10.0 mg of *carbamazepine IPRS* in 5 ml of *methanol* and dilute to 10.0 ml with *water*. Dilute 1.0 ml of the solution to 10.0 ml with the solvent mixture.

Reference solution (b). Dissolve2 mg, each of, *carbamazepine IPRS, carbamazepine related compound A IPRS, carbamazepine related compound B IPRS* in 50 ml of *methanol* and dilute to 100.0 ml with *water*. Dilute 1.0 ml of the solution to 10.0 ml with the solvent mixture.

Chromatographic system

- astainless steel column 10 cm x 2.1 mm, packed with nitrile groups bonded to porous silica (1.8 µm) (Such as Nucleoside CN),
- column temperature: 40º,
- mobile phase: A. add0.5ml of *triethylamine* and 0.5 ml of *formic acid* in 1000 ml of *water*,
  B.add0.25ml of *formic acid* in1000 ml of *methanol*,
- a gradient programme using the conditions given below,
- flow rate: 0.3 ml per minute,
- spectrophotometer set at 230 nm,
- injection volume: 2 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	80	20
3	80	20
12	60	40
18	45	55
20	45	55
20.1	80	20
23	80	20

Name	Relative retention time
Carbamazepine related compound A[1]	0.96
Carbamazepine	1.00
Carbamazepine related compound B[2]	1.45

[1]10,11-Dihydrocarbamazepine,
[2]5*H*-Dibenz[*b*,*f*]azepine.

Inject reference solution (b). The test is not valid unless the resolution between the peaks due to carbamazepine related compound A and carbamazepine is not less than 1.7and the relative standard deviation for replicate injections is not more than 2.0 per cent.

Inject reference solution (b) and test solution (a). In the chromatogram obtained with test solution (a), the area of any peak corresponding to carbamazepine related compound A and carbamazepine related compound Bis not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.2 per cent), the area of any other secondary peak is not more than the area of principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent) and the sum of the areas of all the secondary peaks is not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent). Ignore any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Assay. Change **to**:
Assay. Determine by liquid chromatography (2.4.14), as described under Related substances with the following modifications.

Inject reference solution (a) and (b). The test is not valid unless the resolution between the peaks due to carbamazepine related compound A and carbamazepine is not less than 1.7 in the chromatogram obtained with reference solution (b), the tailing factor is not more than 2.0 and the relative standard deviation for replicate injections is not more than 1.0 per cent in the chromatogram obtained with reference solution (a).

Inject reference solution (a) and test solution (b).

Calculate the content of $C_{15}H_{12}N_2O$.

Carbamazepine Tablets. Page 1732

Identification

Change **to**: **Identification**

A. Boil a quantity of the powdered tablets containing 0.2 g of Carbamazepine with 15 ml of *acetone*, filter the hot solution, wash the filtrate with two 5 ml quantities of hot acetone, cool in ice, evaporate the combined filtrates to dryness. On the residue, determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *carbamazepine IPRS* or with the reference spectrum of carbamazepine.

B. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with reference solution (c).

Related substances. Change **to**:
Related substances. Determine by liquid chromatography (2.4.14).

Solvent mixture. Equal volumes of *methanol* and *water.*

Test solution. Disperse a quantity of the powdered tablets containing 100 mg of Carbamazepine in the solvent mixture, with the aid of ultrasound for 15 minutes and dilute to 100.0 ml with the solvent mixture, filter.

Reference solution (a). A solution containing 0.002 per cent w/v, each of, *carbamazepine IPRS, carbamazepine related compound B IPRS* and*9-methylacridine IPRS* in *methanol*. Dilute 1.0 ml of the solution to 20.0 ml with the solvent mixture.
Reference solution (b). A solution containing 0.01 per cent w/v of *carbamazepine IPRS* and 0.05 per cent w/v of *carbamazepine related compound A IPRS* in *methanol*. Dilute 1.0 ml of the solution to 10.0 ml with the solvent mixture.

Reference solution (c). A 0.2 per cent w/v solution of *carbamazepine IPRS* in *methanol*. Dilute 1.0 ml of the solution to 10.0 ml with the solvent mixture.

Chromatographic system

- astainless steel column 25 cm x 4.6 mm, packed with nitrile groups bonded to porous silica (7 µm) (Such as Nucleosil CN),
- mobile phase: a mixture of 30 volumes of *tetrahydrofuran,* 120 volumes of *methanol* and 850 volumes of *water* add 0.2 volume of *anhydrous formicacid* and 0.5 volume of *triethylamine,*
- flow rate: 1.5 ml per minute,
- spectrophotometer set at 230 nm,
- injection volume: 20 µl.

Name	Relative retention time
9-Methylacridine	0.54
Carbamazepine related compound A[1*]	0.87
Carbamazepine	1.00
Carbamazepine related compound B[2]	3.1

*Process impurity, included for identification only and not to be included in total degradation product,
[1] 10-11- Dihydrocarbamazepine.
[2] 5H-Dibenz[b,f]azepine.

Inject reference solution (a) and (b). The test is not valid unless the resolution between the peaks due to carbamazepine related compound A and carbamazepine is not less than 1.7 in the chromatogram obtained with reference solution (b) and the relative standard deviation for replicate injections is not more than 10.0 per cent, for all the peaks in the chromatogram obtained with reference solution (a).

Inject reference solution (a) and the test solution. Run the chromatogram 3.5 times the retention time of the principal peak. The area of any peak corresponding to carbamazepine related compound B and 9-methylacridine, each of, is not more than twice the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.20 per cent), the area of any other secondary peak is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.20 per cent) and the sum of areas of all the secondary peaks is not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.30 per cent). Ignore any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Assay. Change **to**:
Assay. Determine by liquid chromatography (2.4.14), as described under Related substances with the following modifications.

Test solution. Weigh and powder 20 tablets. Disperse a quantity of the powder containing 200 mg of Carbamazepine in *methanol* with the aid of ultrasound for 15 minutes and dilute to 100.0 ml with *methanol*, filter. Dilute 1.0 ml of the filtrate to 10.0 ml with the solvent mixture.

Inject reference solution (b) and (c). The test is not valid unless the resolution between the peaks due to carbamazepine related compound A and carbamazepine is not less than 1.7 in the chromatogram obtained with reference solution (b) and the relative standard deviation for replicate injections is not more than 2.0 per cent in the chromatogram obtained with reference solution (c).

Inject reference solution (c) and the test solution.

Calculate the content of $C_{15}H_{12}N_2O$ in the tablets.

Carboplatin. Page 1743

Insert before **Category**

CAUTION— Carboplatin is potentially cytotoxic. Great care should be taken in handling the powder and preparing solutions.

Related substances

Change **to**: **Related substances**. Determine by liquid chromatography(2.4.14).

NOTE— Use the solutions within 2 hours.

Test solution. Dissolve 20 mg of the substance under examination in *water* and dilute to 20.0 ml with *water*.

Reference solution (a). A 0.1 per cent w/v solution of *carboplatin IPRS* in *water*.

Reference solution (b). Dilute 5.0 ml of reference solution (a) to 200.0 with *water*. Further, dilute 1.0 ml of the solution to 10.0 ml with *water*.

Chromatographic system
– a stainless steel column 25 cm x 4.6 mm, packed with aminopropylsilane bonded to porous silica (5 µm),
– mobile phase: a mixture of 13 volumes of *water* and87 volumes of *acetonitrile*,
– flow rate: 2 ml per minute,
– spectrophotometer set at 230 nm,
– injection volume: 10 µl.

Name		Relative retention time
Cisplatin[1]	0.3	
Carboplatin		1.0

[1]cis-Diamminedichloroplatinum(II).

Inject reference solution (a). The test is not valid unless the tailing factor is not more than 2.5 and the relative standard deviation for replicate injections is not more than 1.2 per cent.

Inject reference solution (b) and the test solution. Run the chromatogram 2.5 times the retention time of the principal peak. In the chromatogram obtained with the test solution, the area of any peak corresponding to cisplatin is not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.25 per cent), the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.25 per cent) and the sum of the areas of all the secondary peaks is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent). Ignore any peak with an area less than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Assay. Change **to**:

Assay. Determine by liquid chromatography (2.4.14), as described under Related substances with following modifications.

Inject reference solution (a). The test is not valid unless the tailing factor is not more than 2.5 and the relative standard deviation for replicate injections is not more than 1.2 per cent.

Inject reference solution (a) and the test solution.

Calculate the content of $C_6H_{12}N_2O_4Pt$.

Carboxymethylcellulose Eye Drops. Page 1748, Addendum 5152

Para 2
Change **to**: Carboxymethylcellulose Eye Drops contain not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of carboxymethylcellulose sodium.

Identification. B
Change **to**: B. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with the reference solution.

Assay. Change **to:**
Assay. Determine by liquid chromatography (2.4.14).

Test solution. Pool the contents of 5 bottles and prepare a homogeneous composite sample. Transfer2.0 ml of the pooled sample to 100-ml volumetric flask, add 70 ml of *water*, sonicate for 2 minutes and dilute to volume with *water*.

Reference solution. A 0.01 per cent w/v solution of *carboxymethylcellulose sodium IPRS* in *water*.

Chromatographic system
– a stainless steel column 25 cm × 4.6 mm, packed with a strong cation exchange phase based on benzene sulphonic acid groups bonded to porous silica (10 µm) (Such as Partisil10 SCX),
– column temperature: 35º,
– mobile phase: a buffer solution prepared by dissolving6.8 g of *potassium dihydrogen orthophosphate* in 1000 ml of *water*,
– flow rate: 0.5 ml per minute,
– refractive index detector maintained at 35°,
– injection volume: 20 µl.

Inject the reference solution. The test is not valid unless the column efficiency is not less than 250 theoretical plates, the tailing factor is not more than 2.0 and the relative standard deviation for replicate injections is not more than 2.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of carboxymethylcellulose sodium in the eye drops.

Carvedilol. Page 1754
Related substances
Change to: **Related substances**. Determine by liquid chromatography (2.4.14).
Test solution. Dissolve 25 mg of the substances under examination in the mobile phase and dilute to 25.0 ml with the mobile phase.

Reference solution (a). A 0.001 per cent w/v solution of *carvedilol IPRS* in the mobile phase. Dilute 1.0 ml of the solution to 10.0 ml with the mobile phase.

Reference solution (b). A 0.002 per cent w/v solution of *carvedilol impurity C IPRS* in the mobile phase. Dilute 1.0 ml of the solution to 100.0 ml with the mobile phase.

Reference solution (c). A 0.0001 per cent w/v solution of *carvedilol impurity A IPRS* in reference solution (a).

Chromatographic system
- a stainless steel column 15 cm x 4.6 mm, packed with end-capped octylsilane bonded to porous silica (5 µm),
- column temperature: 55°,
- mobile phase: a mixture of 65 volumes of 0.27 per cent w/v solution of *potassium dihydrogen phosphate* in *water*, adjusted to pH 2.0 with *orthophosphoric acid* and 35 volumes of *acetonitrile*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 240 nm,
- injection volume: 20 µl.

Name	Relative retention time	Correction factor
Carvedilol impurity A[1]	0.5	2.0
Carvedilol (Retention time: about 4 minutes)	1.0	--
Carvedilol impurity C[2]	2.9	--
Carvedilol impurity D[3]	3.8	--

[1] 1-[[9-[2-hydroxy-3-[[2-(2-methoxyphenoxy)ethyl]amino]propyl]9*H*-carbazol-4-yl]oxy]-3-[[2-(2-methoxyphenoxy)ethyl]amino]propan-2-ol,
[2] (2RS)-1-[benzyl[2-(2-methoxyphenoxy)ethyl]amino]-3-(9*H*-carbazol—4-yloxy)propan-2-ol,

[3]1-(9*H*-carbazol-4-yloxy)-3-[4-[2-hydroxy-3-[[2-(2-methoxyphenoxy)ethyl]amino]propoxy]-9*H*-carbazol-9-yl]propan-2-ol.

Inject reference solution (b) and (c). The test is not valid unless the resolution between the peak due to carvedilol impurity A and carvedilol is not less than 3.5 in the chromatogram obtained with reference solution (c) and the signal-to-noise ratio is not less than 10 for impurity C in the chromatogram obtained with reference solution (b).

Inject reference solution (a), (b) and the test solution. Run the chromatogram 6 times of carvedilol peak. In the chromatogram obtained with the test solution, the area of any peak corresponding to carvedilol impurity A is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent), the area of any peak corresponding to carvedilol impurity D is not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent), the area of any peak corresponding to carvedilol impurity C is not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.02 per cent), the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent) and the sum of the areas of all the secondary peaks other than carvedilol impurity C is not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent). Ignore any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Carvedilol Tablets. Page 1755

Related substances

Change to: **Related substances**. Determine by liquid chromatography (2.4.14).

Solvent mixture A. 10 volumes of *1M hydrochloric acid* and 90 volumes of *methanol*.

Solvent mixture B. 10 volumes of *water* and 90 volumes of solvent mixture A.

Solvent mixture C. Equal volumes of solvent mixture A and *water*.

Buffer solution. A solution containing 500 volumes of 0.14 per cent w/v of *potassium dihydrogen phosphate* and 10 volumes of *triethylamine*, adjusted to pH 3.0 with *orthophosphoric acid*.

Test solution. Disperse a quantity of the powdered tablets containing 25 mg of Carvedilol in 10 ml of *water* with the aid of ultrasound for 20 minutes, add 70 ml of solvent mixture A and further sonicate for 30 minutes, dilute to 100.0 ml with solvent mixture A, mix and centrifuge. Dilute 1 volume of supernatant liquid to 2 volumes with *water* and filter.

Reference solution (a). A 0.00125 per cent w/v solution of *carvedilol IPRS* in solvent mixture A. Dilute 1.0 ml of the solution to 100.0 ml with solvent mixture A.

Reference solution (b). Dissolve 3.125 mg of *carvedilol impurity C IPRS* in 10 ml of solvent mixture B and dilute to 250.0 ml with 50 per cent v/v of *methanol*. Dilute 1.0 ml of the solution to 10.0 ml with solvent mixture C. Further dilute 1.0 ml of the solution to 50.0 ml with solvent mixture C.

Reference solution (c). A 0.1 per cent w/v solution of *carvedilol for system suitability IPRS* (containing impurity A and D) in 50 per cent v/v of *methanol*.

Chromatographic system

- a stainless steel column 5 cm x 4.6 mm, packed with octylsilane bonded to porous silica (3 µm) (Such as Hypersil MOS-1),
- column temperature: 40°,
- mobile phase: A. a mixture of 7.5 volumes of 0.69 per cent w/v solution of *sodium lauryl sulphate* in the buffer solution, 36 volumes of *acetonitrile* and 56.5 volumes of *water*,
  B. a mixture of 7.5 volumes of 0.69 per cent w/v solution of *sodium lauryl sulphate* in the buffer solution, 45 volumes of *acetonitrile* and 47.5 volumes of *water*,
- a gradient programme using the conditions given below,
- flow rate: 1 ml per minutes,
- spectrophotometer set at 240 nm,
- injection volume: 25 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	100	0
20	100	0
25	0	100
45	0	100
46	100	0

60 100 0

Name	Relative retention time	Correction factor
Carvedilol (Retention time: about 12 minutes)	1.0	--
Carvedilol impurity C[1]	2.5	--
Carvedilol impurity A[2]	2.6	2.0
Carvedilol impurity D[3]	2.7	--

[1](2RS)-1-[benzyl[2-(2-methoxyphenoxy)ethyl]amino]-3-(9*H*-carbazol—4-yloxy)propan-2-ol,
[2]1-[[9-[2-hydroxy-3-[[2-(2-methoxyphenoxy)ethyl]amino]propyl]9*H*-carbazol-4-yl]oxy]-3-[[2-(2-methoxyphenoxy)ethyl]amino]propan-2-ol,
[3]1-(9*H*-carbazol-4-yloxy)-3-[4-[2-hydroxy-3-[[2-(2-methoxyphenoxy)ethyl]amino]propoxy]-9*H*-carbazol-9-yl]propan-2-ol.

Inject reference solution (c) to identify the peaks due to carvedilol impurity A and D.

Inject reference solution (b) and (c). The test is not valid unless the peak-to-valley ratio is not less than 3.5, where Hp is the height above the baseline of the peak due to impurity A and Hv is the height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity D in the chromatogram obtained with reference solution (c) and the signal-to-noise ratio is not less than 10 for the peak due to impurity C in the chromatogram obtained with reference solution (b).

Inject reference solution (a), (b) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to carvedilol impurity C is not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.02 per cent), the area of any other secondary peak is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent) and the sum of the areas of all the secondary peaks, other than carvedilol impurity C is not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent). Ignore any peak with an area less than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent).

Cefixime Tablets. Page 1784

Assay. *Reference solution (a)*, line 1
Change **from**: 0.02 per cent
to: 0.022 per cent

Cefotaxime Sodium. Page 1787

Insert before **Absorbance**
Specific optical rotation(2.4.22). + 58.0 to + 64.0, determined in 1.0 per cent w/v solution in *water*.

Ceftriaxone Sodium. Page 1800

Description
Change **from**: A white or yellowish, crystalline powder, slightlyhygroscopic.
to: A white to yellowish white crystalline powder.

Ceftriaxone Injection. Page 1801

Description
Change **from**:A white or almost white powder.
to:A white to yellowish white powder.

Related substances. *Reference solution (a)*
Change **from**: A 0.03 per cent w/v solution of *ceftriaxone sodium IPRS* in the mobile phase.
to: A solution of *ceftriaxone sodium IPRS* containing 0.03 per cent w/v of ceftriaxone in the mobile phase.

Cefuroxime Axetil Tablets. Page 1804

Assay. *Reference solution (c)*

Change **to**: *Reference solution (c)*. Dissolve a suitable quantity of *cefuroxime axetil IPRS* in *methanol* and dilute with *methanol* to obtain a solution containing 0.3 per cent w/v of Cefuroxime Axetil. Dilute 1.0 ml of the solution to 10.0 ml with the mobile phase.

Cefuroxime Sodium. Page 1806

Assay. *Reference solution*

Change **to**: *Reference solution*. Dissolve 25 mg of *cefuroxime sodium IPRS* in *water* and dilute to 25.0 ml with *water*. Immediately transfer 5.0 ml of the solution to a 100-ml volumetric flask, add 20.0 ml of 0.15 per cent w/v solution of *orcinol* (internal standard) in *water* and dilute to volume with *water*.

After chromatographic system, para 1

Change **to**: Inject the reference solution. The test is not valid unless the resolution between the peaks due to cefuroxime and orcinol (internal standard) is not less than 3.5, the column efficiency is not less than 1300 theoretical plates, the tailing factor is not more than 2.0 for cefuroxime peak and the relative standard deviation of the peak area ratio due to cefuroxime and the internal standard for the replicate injections is not more than 2.0 per cent.

Last line

Change **to**: Calculate the content of $C_{16}H_{15}N_4NaO_8S$, using ratio of the peak area of cefuroxime to that of peak area of the internal standard.

Cefuroxime Injection. Page 1807

Related substances. *Reference solution (a)*

Change **from**: A 0.1 per cent w/v solution of *cefuroxime sodium IPRS* in *water*.

to: A solution of *cefuroxime sodium IPRS* containing 0.1 per cent w/v of *cefuroxime* in *water*.

Assay. *Reference solution*

Change **to**: *Reference solution*. Dissolve an accurately weighed quantity of *cefuroxime sodium IPRS* equivalent to 25 mg of cefuroximein *water* and dilute to 25.0 ml with *water*. Immediately transfer 5.0 ml of the solution to a 100-ml volumetric flask, add 20.0 ml of 0.15 per cent w/v solution of *orcinol* (internal standard) in *water* and dilute to volume with *water*.

After chromatographic system, para 1

Change **to**: Inject the reference solution. The test is not valid unless the resolution between the peaks due to cefuroxime and orcinol (internal standard) is not less than 3.5, the column efficiency is not less than 1300 theoretical plates, the tailing factor is not more than 2.0 for cefuroxime peak and the relative standard deviation of the peak area ratio due to cefuroxime and the internal standard for the replicate injections is not more than 2.0 per cent.

Last line

Change **to**: Calculate the content of $C_{16}H_{16}N_4O_8S$ in the injection using ratio of the peak area of cefuroxime to that of peak area of the internal standard.

Cetostearyl Alcohol Page 1823

Melting range. Delete the requirement.

Cetyl Alcohol. Page 1825

Melting range. Delete the requirement.

Chloramphenicol Ear Drops. Page 1831

Identification. A

Change **to**: A. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with reference solution (a).

Chlorpheniramine Maleate. Page 1857

Para 2, line 2

Change **from**: 101.0 per cent

to: 102.0 per cent

Identification. B

Change **to**: B. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with reference solution (c).

pH

Change **to**: **Optical rotation** (2.4.22). +0.1º to -0.1º, determined in 10.0 per cent w/v solution in *water* at 20º.

Related substances

Change **to**: **Related substances**. Determine by liquid chromatography (2.4.14).

Solution A. Dissolve 5.44 g of *potassium dihydrogen phosphate* in 1000.0 ml of *water*, adjusted to pH 3.0 with *orthophosphoric acid*.

Solvent mixture. 95 volumes of solution A and 5 volumes of *acetonitrile*.

Test solution. Dissolve 50 mg of the substances under examination in the solvent mixture, with the aid of ultrasound and dilute to 100.0 ml with the solvent mixture.

Reference solution (a). A 0.01 per cent w/v solution of *chlorpheniramine maleate IPRS* in the solvent mixture. Dilute 1.0 ml of the solution to 100.0 ml with the solvent mixture.

Reference solution (b). Dilute 2.0 ml of reference solution (a) to 10.0 ml with the solvent mixture.

Reference solution (c). A 0.05 per cent w/v solution of *chlorpheniramine maleate IPRS* in the solvent mixture.

Reference solution (d). A solution containing 0.0002 per cent w/v, each of, *pheniramine maleate IPRS*, *chlorpheniramine related compound B IPRS* and *chlorpheniramine related compound C IPRS* in reference solution (c).

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5µm),
- mobile phase: A. solution A,
  B. *acetonitrile*,
- a gradient programme using the conditions given below,
- flow rate: 1 ml per minute,
- spectrophotometer set at 225 nm,
- injection volume: 10 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	95	5
1	95	5
20	70	30
30	70	30
31	95	5
40	95	5

Name	Relative retention time	Correction factor
Maleic acid[1]	0.18	--
Diamine analog[2]	0.37	1.37
Chlorpheniramine related compound B[3]	0.49	1.30
Pheniramine[4]	0.57	--
Chlorpheniramine related compound C[5]	0.97	--
Chlorpheniramine	1.0	--
Chlorpheniramine nitrile[6]	1.19	--

[1]included for identification only,
[2]2-(4-Chlorophenyl)-4-(dimethylamino)-2-[2-(dimethylamino)ethyl]butanenitrile,
[3]di(pyridine-2-yl)amine,
[4]used only to establish the system suitability,
[5]3-(4-Chlorophenyl)-*N*-methyl-3-(pyridin-2-yl)propan-1-amine,
[6]2-(4-Chlorophenyl)-4-(dimethylamino)-2-(pyridin-2-yl)butanenitrile.

Inject reference solution (a), (b) and (d). The test is not valid unless the resolution between the peaks due to chlorpheniramine related compound C and chlorpheniramine is not less than 1.5 and between the peaks due to

chlorpheniramine related compound B and chlorpheniramine is not less than 2.0 in the chromatogram obtained with reference solution (d), the relative standard deviation for replicate injections is not more than 5.0 per cent for chlorpheniramine in the chromatogram obtained with reference solution (a) and the signal-to-noise ratio is not less than 10 for chlorpheniramine peak in the chromatogram obtained with reference solution (b).

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to diamine analog is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent), the area of any peak corresponding to chlorpheniramine related compound B, chlorpheniramine related compound C and chlorpheniramine nitrile, each of, is not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent), the area of any other secondary peak is not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent) and the sum of the areas of all the secondary peaks is not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent). Ignore the peak due to maleic acid and any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with the reference solution (a) (0.05 per cent).

Assay
Change **to**: **Assay**. Determine by liquid chromatography (2.4.14), as described under Related substances.

Inject reference solution (c) and (d). The test is not valid unless the resolution between the peaks due to chlorpheniramine related compound C and chlorpheniramine is not less than 1.5 and chlorpheniramine related compound B and pheniramine is not less than 2.0 in the chromatogram obtained with reference solution (d), the tailing factor is not more than 2.0and the relative standard deviation for replicate injections is not more than 1.0 per cent in the chromatogram obtained with reference solution (c).

Inject reference solution (c) and the test solution.

Calculate the content of $C_{16}H_{19}ClN_2$, $C_4H_4O_4$.

Cilostazol Tablets. Page 1876

Identification. A
Change **to**: A. To powdered tablets containing 0.1 g of Cilostazol, add 10 ml of *chloroform,* shake for 1 minute, filter and evaporate the filtrate to dryness. Dry the residue at 105º. On the residue, determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum obtained with *cilostazol IPRS* treated in the same manner or with the reference spectrum of cilostazol.

Ciprofloxacin. Page 1882

Identification. B
Change **to**: B. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with reference solution (a).

Related substances
Change **to**: **Related substances**. Determine by liquid chromatography (2.4.14).
Buffer solution. A solution prepared by diluting 3.4 ml of *orthophosphoric acid* in 2000.0 ml of *water*, adjusted to pH 3.0 with *triethylamine*.

Solvent mixture. 13 volumes of *acetonitrile* and 87 volumes of buffer solution.

Test solution. Transfer 35 mg of the substance under examination to a 100-ml volumetric flask, add 0.2 ml of 7 per cent v/v solution of *orthophosphoric acid* and dilute to volume with the solvent mixture.

Reference solution (a). Transfer 7 mg, each of, *fluoroquinolonic acid IPRS* and *ciprofloxacin IPRS* to a 100-ml volumetric flask, add 0.1 ml of *6M ammonium hydroxide* and dilute to volume with *water*. Dilute 1.0 ml of the solution to 100.0 ml with the solvent mixture.

Reference solution (b). A solution containing 0.00075 per cent w/v, each of, *ciprofloxacin ethylenediamine analog IPRS* and *ciprofloxacin IPRS* in the solvent mixture.

Chromatographic system
– a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5µm),
– column temperature: 40˚,
– mobile phase: A. buffer solution,

B. *acetonitrile*,

– a gradient programme using the conditions given below,
– flow rate: 1.5 ml per minute,
– spectrophotometer set at 263 nm and 278 nm,
– injection volume: 30 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	87	13
10	87	13
11	50	50
16	50	50
16.1	87	13
20	87	13

Name	Relative retention time
Ciprofloxacin ethylenediamine analog[1]	0.7
Ciprofloxacin	1.0
Fluoroquinolonic acid[2] (at 263 nm)	1.89

[1]1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-[(2-aminoethyl)amino]-3-quinolinecarboxylic acid hydrochloride,
[2]7-Chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid.

Inject reference solution (a) at 263 nm and 278 nm and reference solution (b) at 278 nm. The test is not valid unless the resolution between the peaks due to ciprofloxacin ethylenediamine analog and ciprofloxacin is not less than 6.0 in the chromatogram obtained with reference solution (b), the tailing factor is not more than 2.0 and the relative standard deviation for replicate injections is not more than 5.0 per cent for ciprofloxacin peak in the chromatogram obtained with reference solution (a) at 278 nm and is not more than 5.0 per cent for fluoroquinolonic acid peak in the chromatogram obtained with reference solution (a) at 263 nm.

Inject reference solution (a) and the test solution at 263 nm. In the chromatogram obtained with the test solution, the area of any peak corresponding to fluoroquinolonic acid is not more than the area of the fluoroquinolonic acid peak in the chromatogram obtained with reference solution (a) (0.2 per cent).

Inject reference solution (a) and the test solution at 278 nm. In the chromatogram obtained with the test solution, the area of any peak corresponding to ciprofloxacin ethylenediamine analog is not more than the area of the ciprofloxacin peak in the chromatogram obtained with reference solution (a) (0.2 per cent), the area of any other secondary peak is not more than the area of ciprofloxacin peak in the chromatogram obtained with reference solution (a) (0.2 per cent), and the sum of areas of all the secondary peaks other than fluoroquinolonic acid is not more than 2.5 times the area of the ciprofloxacin peak in the chromatogram obtained with reference solution (a) (0.5 per cent). Ignore any peak with an area less than 0.25 times the area of ciprofloxacin peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Fluoroquinolonic acid- Delete the requirement

Ciprofloxacin Injection. Page 1883

Identification

Change **to**: In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with reference solution (a).

Ciprofloxacin Hydrochloride. Page 1885

Identification. B

Change **to**: B. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with reference solution (a).

Related substances

Change **to**: **Related substances**. Determine by liquid chromatography (2.4.14).

Buffer solution. A solution prepared by diluting 3.4 ml of *orthophosphoric acid* in 2000.0 ml of *water*, adjusted to pH 3.0 with *triethylamine*.

Solvent mixture. 13 volumes of *acetonitrile* and 87 volumes of buffer solution.

Test solution. Transfer 35 mg of the substance under examination to a 100-ml volumetric flask, add 0.2 ml of 7 per cent v/v solution of *orthophosphoric acid* and dilute to volume with the solvent mixture.

Reference solution (a). Transfer 7 mg, each of, *fluoroquinolonic acid IPRS* and *ciprofloxacin hydrochloride IPRS* to a 100-ml volumetric flask, add 0.1 ml of *6M ammonium hydroxide* and dilute to volume with *water*. Dilute 1.0 ml of the solution to 100.0 ml with the solvent mixture.

Reference solution (b). A solution containing 0.00075 per cent w/v, each of, *ciprofloxacin ethylenediamine analog IPRS* and *ciprofloxacin hydrochloride IPRS* in the solvent mixture.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5µm),
- column temperature: 40˚,
- mobile phase: A. buffer solution,
  B. *acetonitrile*,
- a gradient programme using the conditions given below,
- flow rate: 1.5 ml per minute,
- spectrophotometer set at 263 nm and 278 nm,
- injection volume: 30 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	87	13
10	87	13
11	50	50
16	50	50
16.1	87	13
20	87	13

Name	Relative retention time
Ciprofloxacin ethylenediamine analog[1]	0.7
Ciprofloxacin	1.0
Fluoroquinolonic acid[2] (at 263 nm)	1.89

[1]1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-[(2-aminoethyl)amino]-3-quinolinecarboxylic acid hydrochloride,
[2]7-Chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid.

Inject reference solution (a) at 263 nm and 278 nm and reference solution (b) at 278 nm. The test is not valid unless the resolution between the peaks due to ciprofloxacin ethylenediamine analog and ciprofloxacin is not less than 6.0 in the chromatogram obtained with reference solution (b), the tailing factor is not more than 2.0 and the relative standard deviation for replicate injections is not more than 5.0 per cent for ciprofloxacin peak in the chromatogram obtained with reference solution (a) at 278 nm and is not more than 5.0 per cent for fluoroquinolonic acid peak in the chromatogram obtained with reference solution (a) at 263 nm.

Inject reference solution (a) and the test solution at 263 nm. In the chromatogram obtained with the test solution, the area of any peak corresponding to fluoroquinolonic acid is not more than the area of the fluoroquinolonic acid peak in the chromatogram obtained with reference solution (a) (0.2 per cent).

Inject reference solution (a) and the test solution at 278 nm. In the chromatogram obtained with the test solution, the area of any peak corresponding to ciprofloxacin ethylenediamine analog is not more than the area of the ciprofloxacin peak in the chromatogram obtained with reference solution (a) (0.2 per cent), the area of any other secondary peak is not more than the area of ciprofloxacin peak in the chromatogram obtained with reference solution (a) (0.2 per cent), and the sum of areas of all the secondary peaks other than fluoroquinolonic acid is not more than 2.5 times the area of the ciprofloxacin peak in the chromatogram obtained with reference solution (a) (0.5 per cent). Ignore any peak with an area less than 0.25 times the area of ciprofloxacin peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Fluoroquinolonic acid- Delete the requirement

Ciprofloxacin Eye Drops. Page 1886

Insert before **Other tests**

Related substances. Determine by liquid chromatography (2.4.14).
Solution A. A 0.29 per cent v/v solution of *orthophosphoric acid* in *water*, adjusted to pH 5.2 with *triethylamine*.

Test solution. Dilute a suitable volume of eye drops containing 10 mg of ciprofloxacin to 50.0 ml with the mobile phase.
Reference solution (a). A 0.0001 per cent w/v solution of *ciprofloxacin hydrochloride IPRS* in the mobile phase.

Reference solution (b). A solution containing 0.0002 per cent w/v, each of, *ciprofloxacin hydrochloride IPRS* and *ciprofloxacin ethylenediamine analog IPRS* in the mobile phase.

Reference solution (c). Dilute 1.0 ml of reference solution (a) to 5.0 ml with the mobile phase.

Chromatographic system
– a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm),
– column temperature: 40°,
– sample temperature: 4°,
– mobile phase: a mixture of 12 volumes of *acetonitrile* and 88 volumes of solution A,
– flow rate: 1 ml per minute,
– spectrophotometer set at 278 nm,
– injection volume: 20 µl.

Name	Relative retention time	Correction factor
Ciprofloxacin ethylenediamine analog[1]	0.7	0.74
Ciprofloxacin1.0	---	

[1]1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-[(2-aminoethyl)amino]-3-quinolinecarboxylic acid hydrochloride.

Inject reference solution (a), (b) and (c). The test is not valid unless the resolution between the peaks due to ciprofloxacin ethylenediamine analog and ciprofloxacin is not less than 6.0 in the chromatogram obtained with reference solution (b), the relative standard deviation for replicate injections is not more than 5.0 per cent in the chromatogram obtained with reference solution (a) and the signal-to-noise ratio is not less than 10 in the chromatogram obtained with reference solution (c).

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to ciprofloxacin ethylenediamine analog is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent), the area of any other secondary peak is not more than 0.4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent) and the sum of the areas of all the secondary peaks is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent).

Assay
Change **to**: **Assay**. Determine by liquid chromatography (2.4.14).

Test solution. Dilute a suitable volume of eye drops containing 5 mg of ciprofloxacin to 50.0 ml with the mobile phase.

Reference solution. A 0.01 per cent w/v solution of *ciprofloxacin hydrochloride IPRS* in the mobile phase.

Use chromatographic system as described under Related substances.

Inject the reference solution. The test is not valid unless the tailing factor is not more than 2.0and the relative standard deviation for replicate injections is not more than 2.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{17}H_{18}FN_3O$ in the eye drops.

Ciprofloxacin Tablets. Page 1886

Identification. B
B. Delete the requirement.

Insert before **Other tests**
Related substances. Determine by liquid chromatography (2.4.14).
Test solution. Disperse a quantity of the powdered tablets containing 45 mg of ciprofloxacin in the mobile phase, with the aid to ultrasound and dilute to 100.0 ml with the mobile phase.

Reference solution (a). A 0.0001 per cent w/v solution of *ciprofloxacin hydrochloride IPRS* in the mobile phase.

Reference solution (b). A solution containing 0.0002 per cent w/v, each of, *ciprofloxacin hydrochloride IPRS* and *ciprofloxacin ethylenediamine analog IPRS* in the mobile phase.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm),
- mobile phase: a mixture of 13 volumes of *acetonitrile* and 87 volumes of *0.025 M orthophosphoric acid*, adjusted to pH 3.0 with *triethylamine*,
- flow rate: 1.5 ml per minute,
- spectrophotometer set at 278 nm,
- injection volume: 10 µl.

Name	Relative retention time
Ciprofloxacin ethylenediamine analog[1]	0.68
Ciprofloxacin	1.0
7-chloro-6-piperazinyl analog[2]	1.2
Chlorociprofloxacin[3]	2.0

[1]1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-[(2-aminoethyl)amino]-3-quinolinecarboxylic acid hydrochloride,
[2]7-chloro-1-cyclopropyl-4-oxo-6-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid,
[3]6-chloro-1-cyclopropyl-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid.

Inject reference solution (a) and (b). The test is not valid unless the resolution between the peaks due to ciprofloxacin ethylenediamine analog and ciprofloxacin is not less than 6.0 in the chromatogram obtained with reference solution (b) and the relative standard deviation for replicate injections is not more than 10 per cent in the chromatogram obtained with reference solution (a).

Inject the test solution. The area of any peak corresponding to ciprofloxacin ethylenediamine analog is not more than 0.5 per cent, the area of any peak corresponding to 7-chloro-6-piperazinyl analog and chlorociprofloxacin, each of, is not more than 0.3 per cent, the area of any other secondary peak is not more than 0.2 per cent and the sum of the areas of all the secondary peaks is not more than 1.0 per cent, calculated by area normalization.

Assay
Change **to**: **Assay**. Determine by liquid chromatography (2.4.14).

Solvent mixture. 87 volumes of *0.025 M phosphoric acid*, adjusted to pH 2.0 with *triethylamine* and 13 volumes of *acetonitrile*.

Test solution. Weigh and powder 20 tablets. Disperse a quantity of the powder containing 0.2 g of ciprofloxacin in 80 ml of the solvent mixture, with the aid of ultrasound for 20 minutes, dilute to 100.0 ml with the solvent mixture. Dilute 2.0 ml of the solution to 20.0 ml with the solvent mixture.

Reference solution (a). A 0.02 per cent w/v solution of *ciprofloxacin hydrochloride IPRS* in the solvent mixture.

Reference solution (b). A 0.005 per cent w/v solution of *ciprofloxacin ethylenediamine analog IPRS* in reference solution (a).

Use the chromatographic system as described under Related substances.

The relative retention time with reference to ciprofloxacin, for ciprofloxacin ethylenediamine analog is about 0.7.

Inject reference solution (a) and (b). The test is not valid unless the resolution between the peaks due to ciprofloxacin ethylenediamine analog and ciprofloxacin is not less than 6 in the chromatogram obtained with reference solution (b), the tailing factor is not more than 2.0and the relative standard deviation for replicate injections is not more than 1.5 per cent in the chromatogram obtained with reference solution (a).

Inject reference solution (a) and the test solution.

Calculate the content of $C_{17}H_{18}FN_3O_3$ in the tablets.

Cisplatin Injection. Page 1889

Trichloroammineplatinate. Delete the requirement

Transplatin. Delete the requirement

Insert before **Bacterial endotoxins**
Related substances. Determine by liquid chromatography (2.4.14).

NOTE- Prepare the solutions immediately before use and protected from light.

Saline solution. A 0.9 per cent w/v solution of *sodium chloride* in *water.*

Test solution. Use the injection, dilute if necessary, with the saline solution to obtain a solution containing 0.05 per cent w/v of Cisplatin.

Reference solution (a). A 0.0001 per cent w/v solution of *cisplatin IPRS* in the saline solution.

Reference solution (b). Dissolve a quantity of *potassium trichloroammineplatinate IPRS (cisplatin impurity B)*in the saline solution to obtain a solution containing 0.0015 per cent w/v of trichloroammineplatinate.

Reference solution (c). A 0.001 per cent w/v solution of *transplatin IPRS (cisplatin impurity A)*in the saline solution.

Reference solution (d). A solution containing 0.001 per cent w/v, each of, *transplatin IPRS, potassium trichloroammineplatinate IPRS* and *cisplatin IPRS* in the saline solution.

Chromatographic system
- a stainless steel column 25 cm x 4.0 mm, packed with base deactivated octylsilane bonded to porous silica (4 µm) (Such as Superspher RP B),
- column temperature 30º,
- mobile phase: dissolve 1.08 g of *sodium octanesulphonate,* 1.7 g of *tetrabutylammonium hydrogen sulphate* and 2.72 g of *potassium dihydrogen phosphate* in 950 ml of *water.* Adjusted to pH 5.9 with *1 M sodium hydroxide* and dilute to 1000 ml with *water,*
- flow rate: 1 ml per minute,
- spectrophotometer set at 210 nm,
- injection volume: 20 µl.

Name	Relative retention time
Cisplatin impurity A[1]	0.6
Cisplatin impurity B[2]	0.7
Cisplatin (retention time: about 4 minutes)	1.0
Cisplatin aquo complex	1.2

[1]transplatin,
[2]potassium trichloroammineplatinate.

Inject the saline solution to identify the displacement peak (the last eluting peak in the group of injection peaks).

Inject reference solution (d). The test is not valid unless the resolution between the peaks due to transplatin (cisplatin impurity A) and potassium trichloroammineplatinate(cisplatin impurity B)is not less than 2.5 and the displacement peak and transplatin (cisplatin impurity A) peak are well separated.

Inject reference solution (a), (b), (c) and the test solution. Run the chromatogram 7 times the retention time of the principal peak. In the chromatogram obtained with the test solution, the area of any peak corresponding to trichloroammineplatinate is not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (3.0 per cent), the area of any peak corresponding totransplatin(cisplatin impurity A) is not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (2.0 per cent),the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent) and the sum of the areas of all other secondary peaks is not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent). Ignore the displacement peak, any peak due to the cisplatin aquo complex and any peak less than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent).

Cisplatin for Injection. Page 1890

Trichloroammineplatinate. Delete the requirement

Transplatin. Delete the requirement

Insert before **Bacterial endotoxins**
Related substances. Determine by liquid chromatography (2.4.14).

NOTE- Prepare the solutions immediately before use and protected from light.

Saline solution. A 0.9 per cent w/v solution of *sodium chloride* in *water.*

Test solution. Dissolve the contents of a sealed container in the saline solution to obtain a solution containing 0.05 per cent w/v of Cisplatin.

Reference solution (a). A 0.0001 per cent w/v solution of *cisplatin IPRS* in the saline solution.

Reference solution (b). Dissolve a quantity of *potassium trichloroammineplatinate IPRS (cisplatin impurity B)* in the saline solution to obtain a solution containing 0.0015 per cent w/v of trichloroammineplatinate.

Reference solution (c). A 0.001 per cent w/v solution of *transplatin IPRS (cisplatin impurity A)* in the saline solution.

Reference solution (d). A solution containing 0.001 per cent w/v, each of, *transplatin IPRS, potassium trichloroammineplatinate IPRS* and *cisplatin IPRS* in the saline solution.

Chromatographic system
- a stainless steel column 25 cm x 4.0 mm, packed with base deactivated octylsilane bonded to porous silica (4 µm) (Such as Superspher RP B),
- mobile phase: dissolve 1.08 g of *sodium octanesulphonate,* 1.7 g of *tetrabutylammonium hydrogen sulphate* and 2.72 g of *potassium dihydrogen phosphate* in 950 ml of *water.* Adjusted to pH 5.9 with *1 M sodium hydroxide* and dilute to 1000 ml with *water,*
- flow rate: 1 ml per minute,
- spectrophotometer set at 210 nm,
- injection volume: 20 µl.

Name	Relative retention time
Cisplatin impurity A[1]	0.6
Cisplatin impurity B[2]	0.7
Cisplatin (retention time: about 4 minutes)	1.0
Cisplatin aquo complex	1.2

[1]transplatin,
[2]potassium trichloroammineplatinate.

Inject the saline solution to identify the displacement peak (the last eluting peak in the group of injection peaks).

Inject reference solution (d). The test is not valid unless the resolution between the peaks due to transplatin (cisplatin impurity A) and potassium trichloroammineplatinate(cisplatin impurity B)is not less than 2.5 and the displacement peak and transplatin (cisplatin impurity A) peak are well separated.

Inject reference solution (a), (b), (c) and the test solution. Run the chromatogram 7 times the retention time of the principal peak. In the chromatogram obtained with the test solution, the area of any peak corresponding to trichloroammineplatinate is not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (3.0 per cent), the area of any peak corresponding totransplatin(cisplatin impurity A) is not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (2.0 per cent),the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent) and the sum of the areas of all other secondary peaks is not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent). Ignore the displacement peak, any peak due to the cisplatin aquo complex and any peak less than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent).

Clarithromycin. Page 1898
Heavy metals

Change **to**: **Heavy metals** (2.3.13). 1.0 g complies with the limit test for heavy metals, Method B (20 ppm).

Insert before **Water**
Sulphated ash (2.3.18).Not more than 0.2 per cent.

Clindamycin Palmitate Hydrochloride Oral Suspension. Page 1908

Assay. *Test solution*, line 1
Change **from**: Transfer 5 ml of the constituted solution
to: Weigh and transfer 5 ml of the constituted suspension

Clobetasol Propionate. Page 1913

Related substances
Change **to**: **Related substances**. Determine by liquid chromatography (2.4.14).
Test solution (a). Dissolve 20 mg of the substance under examination in the mobile phase and dilute to 20.0 ml with the mobile phase.

Test solution (b). Dilute 5.0 ml of test solution (a) to 25.0 ml with the mobile phase.

Reference solution (a). A 0.02 per cent w/v solution of *clobetasol propionate IPRS* in the mobile phase.

Reference solution (b). Dilute 1.0 ml of reference solution (a) to 200.0 ml with the mobile phase.

Reference solution (c). Dissolve the contents of a vial of *clobetasol impurity J IPRS* in 2.0 ml of the mobile phase. To 0.5 ml of the solution, add 0.5 ml of reference solution (a) and dilute to 20.0 ml with the mobile phase.

Reference solution (d). Dissolve the contents of a vial of *clobetasol propionate for peak identification IPRS* (containing impurities A, B, D and E) in 2 ml of the mobile phase.

Chromatographic system
- a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm),
- column temperature: 30°,
- mobile phase: a mixture of 42.5 volumes of a buffer solution prepared by dissolving7.85 g of *sodium dihydrogen orthophosphate monohydrate* in 1000 ml of *water*, adjusted to pH 5.5 with 10 per cent w/v solution of *sodium hydroxide*, 47.5 volumes of *acetonitrile* and 10 volumes of *methanol*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 240 nm,
- injection volume: 10 µl.

Name	Relative retention time	Correction factor
Clobetasol impurity A[1]	0.4	---
Clobetasol impurity B[2]	0.6	0.6
Clobetasol (Retention time: about 11 minute)	1.0	---
Clobetasol impurity J[3]	1.1	---
Clobetasol impurity D[4]	1.2	---
Clobetasol impurity E[5]	2.1	---

[1]9-fluoro-11β,21-dihydroxy-16β-methyl-3,20-dioxopregna-1,4-dien-17-yl propanoate (betamethasone 17-propionate),
[2]21-chloro-9-fluoro-11β-hydroxy-16-methylpregna-1,4,16-triene-3,20-dione,
[3](17*R*)-4′-chloro-5′-ethyl-9-fluoro-11β-hydroxy-16β-methylspiro[androsta-1,4-diene-17,2′-furan]-3,3′-dione (17α-spiro compound),
[4]21-chloro-9-fluoro-11β-hydroxy-16β-methyl-3,20-dioxopregn-4-en-17-yl propanoate (1,2-dihydroclobetasol 17-propionate),
[5]21-chloro-16β-methyl-3,20-dioxopregna-1,4-dien-17-yl propanoate.

Inject reference solution (c) and (d) to identify the peaks due to clobetasol impurity J and clobetasol impurity A, B, D and E, respectively.

Inject reference solution (c). The test is not valid unless the resolution between the peaks due to clobetasol propionate and clobetasol impurity J is not less than 2.0.

Inject reference solution (b) and test solution (a). Run the chromatogram 3 times the retention time of the principal peak. In the chromatogram obtained with test solution (a), the area of any peak corresponding to clobetasol impurity B and E, each of, is not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent), the area of any peak corresponding to clobetasol impurity A and D, each of, is not more than twice the area

of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent), the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent) and the sum of the areas of all the secondary peaks is not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent). Ignore any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Assay
Change **to**: **Assay**. Determine by liquid chromatography (2.4.14), as described under Related substances with following modification.

Inject reference solution (a) and test solution (b).

Calculate the content of $C_{25}H_{32}ClFO_5$.

Clobetasol Cream. Page 1914

Identification. B, line 2
Change **from**: test solution (a)
to: the test solution

Assay
Change **to**: **Assay**. Determine by liquid chromatography (2.4.14).

CAUTION- Prepare the test solution with full facial protection and wearing heat-resistant gloves.

Internal standard solution. A 0.02 per cent w/v solution of *beclomethasone dipropionate IPRS* in *ethanol.*

Test solution. Disperse a quantity of the cream containing 1 mg of Clobetasol Propionate in 10 ml of *ethanol*, stopper firmly using a plastic stopper, heat on a water-bath with intermittent shaking until the cream is completely dispersed. Cool the contents in ice for 30 minutes, centrifuge. Transfer 5.0 ml of the supernatant liquid to 10-ml volumetric flask and dilute to volume with the internal standard solution.

Reference solution. A 0.025 per cent w/v solution of *clobetasol propionate IPRS* in *ethanol.* Transfer 2.0 ml of the solution to a 10-ml volumetric flask, add 5 ml of the internal standard solution and dilute to volume with *ethanol.*

Chromatographic system
– a stainless steel column 10 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm),
– column temperature: 60°,
– mobile phase: a mixture of 45 volumes of *ethanol* and 55 volumes of *water*,
– flow rate: 2 ml per minute,
– spectrophotometer set at 240 nm,
– injection volume: 10 µl.

Inject the reference solution and the test solution.

Calculate the content of $C_{25}H_{32}ClFO_5$ in the cream from the peak area ratio of clobetasol propionate to the internal standard in the chromatogram obtained with the reference solution and the test solution.

Clobetasol Ointment. Page 1915

Identification. B, line 3
Change **from**: reference solution (a)
to: the reference solution

Assay
Change **to**: **Assay**. Determine by liquid chromatography (2.4.14).

CAUTION- Prepare the test solution with full facial protection and wearing heat-resistant gloves.

Internal standard solution. A 0.02 per cent w/v solution of *beclomethasone dipropionate IPRS* in *ethanol.*

Test solution. Disperse a quantity of the ointment containing 1 mg of Clobetasol Propionate in 10 ml of *ethanol*, stopper firmly using a plastic stopper, heat on a water-bath with intermittent shaking until the ointment is completely dispersed. Cool the contents in ice for 30 minutes, centrifuge. Transfer 5.0 ml of the supernatant liquid to 10-ml volumetric flask and dilute to volume with the internal standard solution.

Reference solution. A 0.025 per cent w/v solution of *clobetasol propionate IPRS* in *ethanol.* Transfer 2.0 ml of the solution to a 10-ml volumetric flask, add 5 ml of the internal standard solution and dilute to volume with *ethanol.*

Chromatographic system
- a stainless steel column 10 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm),
- column temperature: 60°,
- mobile phase: a mixture of 45 volumes of *ethanol* and 55 volumes of *water*,
- flow rate: 2 ml per minute,
- spectrophotometer set at 240 nm,
- injection volume: 10 µl.

Inject the reference solution and the test solution.

Calculate the content of $C_{25}H_{32}ClFO_5$ in the ointment from the peak area ratio of clobetasol propionate to the internal standard in the chromatogram obtained with the reference solution and the test solution.

Clonazepam. Page 1924

Para 2

Change **to**: Clonazepam contains not less than 98.0 per cent and not more than 102.0 per cent of $C_{15}H_{10}ClN_3O_3$, calculated on the dried basis.

Related substances. Change **to**:
Related substances. Determine by liquid chromatography (2.4.14).

Solvent mixture. 13 volumes of *tetrahydrofuran*,52 volumes of *methanol* and 60 volumes of *water.*

Test solution. Dissolve 10 mg of the substance under examination in the solvent mixture and dilute to 100.0 ml with the solvent mixture.
Reference solution (a). A 0.01 per cent w/v solution of *clonazepam IPRS* in the solvent mixture.

Reference solution (b). Dilute 1.0 ml of reference solution (a) to 100.0 ml with the solvent mixture.

Reference solution (c). A solution containing 0.004 per cent w/v, each of, *clonazepam related compound A IPRS, clonazepam related compound B IPRS* and *clonazepam IPRS* in the solvent mixture.

Chromatographic system
- a stainless steel column 15 cm x 4.6 mm, packed with octylsilane bonded to porous silica (5 µm),
- mobile phase: a mixture of 60 volumes of a buffer solution prepared by dissolving 6.6 g of *dibasic ammonium phosphate* in 950 ml of *water*, adjusted to pH 8.0 with *1M orthophosphoric acid* or *1M sodium hydroxide* and diluted to 1000 ml with *water,* 52 volumes of *methanol* and 13 volumes of *tetrahydrofuran*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 50 µl.

Name	Relative retention time	Correction factor
Clonazepam	1.0	---
Clonazepam related compound A[1]	2.2	1.84
Clonazepam related compound B[2]	2.5	0.94

[1]3-Amino-4-(2-chlorophenyl)-6-nitrocarbostyril,
[2]2-Amino-2′-chloro-5-nitrobenzophenone.

Inject reference solution (b) and (c). The test is not valid unless the resolution between the peaks due to clonazepam related compound A and clonazepam related compound B is not less than 2.0 in the chromatogram obtained with reference solution (c), the tailing factor is not more than 1.5 and the relative standard deviation for replicate injection is not more than 5.0 per cent in the chromatogram obtained with reference solution (b).

Inject reference solution (b) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to clonazepam related compound A and B ,each of, is not more than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent), the area of any other secondary peak is not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent) and the sum of areas of all other secondary peaks is not more than 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent).

Clonazepam related compound C. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel GF254.*

Mobile phase. A mixture of 60 volumes of *acetone* and40 volumes of *n-heptane.*

Test solution. Dissolve 0.25 g of the substance under examination in *acetone* and dilute to 10.0 ml with *acetone.*

Reference solution. A 0.005 per cent w/v solution of *clonazepam related compound C IPRS* in *acetone.*

Apply to the plate 20 µl of each solution. After development, dry the plate in air and heavily spray with *2M sulphuric acid* and dry at 105º for 15 minutes and successively spray the plate with the *0.01 M sodium nitrite*, 0.009 M *ammonium sulphamate* and 0.1 per cent w/v solution of *N-(1-naphthyl)ethylenediamine dihydrochloride* in a mixture of 70 volumes of *acetone* and 30 volumes of *water* and dry the plate with a current of air. Any secondary spot in the chromatogram obtained with the test solution is not more intense than the spot in the chromatogram obtained with the reference solution (0.2 per cent).

Assay. Change **to**:
Assay. Determine by liquid chromatography (2.4.14), as described under Related substances with the following modifications.

Inject reference solution (b) and (c). The test is not valid unless the resolution between the peaks due to clonazepam related compound A and clonazepam related compound B is not less than 2.0 in the chromatogram obtained with reference solution (c), the tailing factor is not more than 1.5 and the relative standard deviation for replicate injections is not more than 2.0 per cent in the chromatogram obtained with reference solution (b).

Inject reference solution (a) and the test solution.

Calculate the content of $C_{15}H_{10}ClN_3O_3$.

Clonazepam Injection. Page 1924

Insert before **Identification**
Usual strength. Concentrate, 1 mg per ml**.**

Identification
Change **to**: In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with reference solution (a).

Related substances. Change **to**:
Related substances. Determine by liquid chromatography (2.4.14).

Solvent mixture. 13 volumes of *tetrahydrofuran,* 52 volumes of *methanol* and 60 volumes of *water.*

Test solution. Dilute a suitable volume of the concentrate with the solvent mixture to obtain a solution containing 0.01 per cent w/v of Clonazepam.

Reference solution (a). A 0.01 per cent w/v solution of *clonazepam IPRS* in the solvent mixture.

Reference solution (b). Dilute 1.0 ml of reference solution (a) to 100.0 ml with the solvent mixture.

Reference solution (c). A solution containing 0.004 per cent w/v, each of, *clonazepam related compound A IPRS, clonazepam related compound B IPRS* and *clonazepam IPRS* in the solvent mixture.

Reference solution (d). Dilute 1.0 ml of reference solution (b) to 10.0 ml with the solvent mixture.

Chromatographic system
- a stainless steel column 15 cm x 4.6 mm, packed with octylsilane bonded to porous silica (5 µm),
- mobile phase: a mixture of 60 volumes of a buffer solution prepared by dissolving 6.6 g of *dibasic ammonium phosphate* in 950 ml of *water*, adjusted to pH 8.0 with *1M orthophosphoric acid* or *1M sodium hydroxide* and diluted to 1000 ml with *water,* 52 volumes of *methanol* and 13 volumes of *tetrahydrofuran*,
- flow rate: 1 ml per minute,

- spectrophotometer set at 254 nm,
- injection volume: 50 µl.

Name	Relative retention time	Correction factor
Unspecified impurity*	0.7	2.44
Clonazepam	1.0	---
Clonazepam related compound A[1]	2.2	1.85
Clonazepam related compound B[2]	2.5	0.91

*may not be present in all formulation,
[1]3-Amino-4-(2-chlorophenyl)-6-nitrocarbostyril,
[2]2-Amino-2′-chloro-5-nitrobenzophenone.

Inject reference solution (a), (c) and (d). The test is not valid unless the resolution between the peaks due to clonazepam related compound A and clonazepam related compound B is not less than 2.0 in the chromatogram obtained with reference solution (c),the tailing factor is not more than 1.5, the relative standard deviation for replicate injections is not more than 2.0 per cent in the chromatogram obtained with reference solution (a) and the signal-to-noise ratio is not less than 10 in the chromatogram obtained with reference solution (d).

Inject reference solution (b) and the test solution. In the chromatogram obtained with the test solution, the area of unspecified impurity at RRT about 0.7 is not more than 0.8 times the area of principal peak in the chromatogram obtained with reference solution (b) (0.8 per cent), the area of any peak corresponding to clonazepam related compound A is not more than 0.4 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.4 per cent), the area of any peak corresponding to clonazepam related compound B is not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent), the area of any other secondary peak is not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent) and the sum of areas of all the secondary peaks, other than unspecified impurity at RRT about 0.7, clonazepam related compound A and clonazepam related compound B is not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent). Ignore any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with the reference solution (b) (0.1 per cent).

Assay. Change **to**:
Assay. Determine by liquid chromatography (2.4.14), as described under Related substances with the following modifications.

Inject reference solution (a) and (c). The test is not valid unless the resolution between the peaks due to clonazepam related compound A and clonazepam related compound B is not less than 2.0 in the chromatogram obtained with reference solution (c), the tailing factor is not more than 1.5 and the relative standard deviation for replicate injections is not more than 1.0 per cent in the chromatogram obtained with reference solution (a).

Inject reference solution (a) and the test solution.

Calculate the content of $C_{15}H_{10}ClN_3O_3$ in the injection.

Clonazepam Tablets. Page 1925

Identification. B, line 3
Change **from**: with the reference solution.
to: with reference solution (a).

Related substances. Change **to**:
Related substances. Determine by liquid chromatography (2.4.14).

Solvent mixture. 13 volumes of *tetrahydrofuran,* 52 volumes of *methanol* and 60 volumes of *water.*

Test solution. Weigh and powder 20 tablets. Disperse a quantity of the powder containing 10 mg of Clonazepam in the solvent mixture and dilute to 100.0 ml with the solvent mixture and filter.

Reference solution (a). A 0.01 per cent w/v solution of *clonazepam IPRS* in the solvent mixture.

Reference solution (b). Dilute 1.0 ml of reference solution (a) to 100.0 ml with the solvent mixture.

Reference solution (c). A solution containing 0.004 per cent w/v, each of, *clonazepam related compound A IPRS, clonazepam related compound B IPRS* and *clonazepam IPRS* in the solvent mixture.

Reference solution (d). Dilute 1.0 ml of reference solution (b) to 10.0 ml with the solvent mixture.

Chromatographic system
- a stainless steel column 15 cm x 4.6 mm, packed with octylsilane bonded to porous silica (5 µm),
- mobile phase: a mixture of 60 volumes of a buffer solution prepared by dissolving 6.6 g of *dibasic ammonium phosphate* in 950 ml of *water*, adjusted to pH 8.0 with *1M orthophosphoric acid* or *1M sodium hydroxide* and diluted to 1000 ml with *water,* 52 volumes of *methanol* and 13 volumes of *tetrahydrofuran*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 50 µl.

Name	Relative retention time	Correction factor
Unspecified impurity*	0.7	2.44
Clonazepam	1.0	---
Clonazepam related compound A[1]	2.2	1.85
Clonazepam related compound B[2]	2.5	0.91

*may not be present in all formulation,
[1]3-Amino-4-(2-chlorophenyl)-6-nitrocarbostyril,
[2]2-Amino-2′-chloro-5-nitrobenzophenone.

Inject reference solution (a), (c) and (d). The test is not valid unless the resolution between the peaks due to clonazepam related compound A and clonazepam related compound B is not less than 2.0 in the chromatogram obtained with reference solution (c),the tailing factor is not more than 1.5, the relative standard deviation for replicate injections is not more than 2.0 per cent in the chromatogram obtained with reference solution (a) and the signal-to-noise ratio is not less than 10 in the chromatogram obtained with reference solution (d).

Inject reference solution (b) and the test solution. In the chromatogram obtained with the test solution, the area of unspecified impurity at RRT about 0.7 is not more than 0.8 times the area of principal peak in the chromatogram obtained with reference solution (b) (0.8 per cent), the area of any peak corresponding to clonazepam related compound A is not more than 0.4 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.4 per cent), the area of any peak corresponding to clonazepam related compound B is not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent), the area of any other secondary peak is not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent) and the sum of areas of all the secondary peaks, other than unspecified impurity at RRT about 0.7, clonazepam related compound A and clonazepam related compound B is not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent). Ignore any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with the reference solution (b) (0.1 per cent).

Assay. Change **to**:
Assay. Determine by liquid chromatography (2.4.14), as described under Related substances with the following modifications.

Inject reference solution (a) and (c). The test is not valid unless the resolution between the peaks due to clonazepam related compound A and clonazepam related compound B is not less than 2.0 in the chromatogram obtained with reference solution (c),the tailing factor is not more than 1.5 and the relative standard deviation for replicate injections is not more than 1.0 per cent in the chromatogram obtained with reference solution (a).

Inject reference solution (a) and the test solution.

Calculate the content of $C_{15}H_{10}ClN_3O_3$ in the tablets.

Clonidine Hydrochloride. Page 1927

Identification. B
Change **to**: When examined in the range 230 nm to 350 nm (2.4.7), a 0.03 per cent w/v solution in *0.01M hydrochloric acid* shows absorption maxima, at about 272 nm and 279 nm and an inflection at about 265 nm; specific absorbance at 272 nm is about 18 and at 279 nm is about 16.

Sulphated ash
Change **from**: 0.2 per cent
to: 0.1 per cent

Assay. Para 1,
Insert at the end.

Carry out a blank titration.

Clopidogrel and Aspirin Tablets. Page 1933

Insert synonym
Clopidogrel Bisulphate and Aspirin Tablets

Para 1
Change **to**: Clopidogrel and Aspirin Tablets contain Clopidogrel Bisulphate equivalent to not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of clopidogrel $C_{16}H_{16}ClNO_2S$ and aspirin $C_9H_8O_4$.

Related substances
For Clopidogrel –
Reference solution (a) and *Reference solution (b)*
Change **to**: *Reference solution.* A 0.00065 per cent w/v solution of *clopidogrel bisulphate IPRS* in the mobile phase.

After chromatographic system, para 1, line 1
Change **from**: Inject reference solution (a).
to: Inject the reference solution.

Last para, line 1, 4, 7 & 10
Change **from**: reference solution (b)
to: the reference solution

Insert at the end.
Labelling. The label states the quantity of clopidogrel bisulphate in terms of the equivalent amount of clopidogrel and aspirin.

Clotrimazole. Page 1935

Identification. B
Change **to:** B. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with reference solution (a).

Related substances. *Reference solution (a)*
Change **to:** *Reference solution (a).* A 0.01 per cent w/v solution of *clotrimazole IPRS* in *acetonitrile*.

Reference solution (c)
Change **to:** *Reference solution (c).* A solution containing 0.001 per cent w/v of *clotrimazole IPRS* and 0.0002 per cent w/v, each of, *clotrimazole impurity A IPRS, clotrimazole impurity B IPRS, clotrimazole impurity D IPRS, clotrimazole impurity E IPRS* and 0.0001 per cent w/v of *clotrimazole impurity F IPRS* in *acetonitrile*.

After Impurity table, para 1 and 2
Change **to:** Inject reference solution (c) to identify the peaks due to clotrimazole impurity A, B, D, E and F.

Inject reference solution (a) and (c). The test is not valid unless the resolution between the peaks due to clotrimazole impurity F and clotrimazole is not less than 4.0 in the chromatogram obtained with reference solution (c), the column efficiency is not less than 2000 theoretical plates and tailing factor is not more than 2.0 in the chromatogram obtained with reference solution (a).

Inject reference solution (b), (c) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to clotrimazole impurity A and B, each of, is not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.2 per cent), the area of any peak corresponding to clotrimazole impurity D and E, each of, is not more than the area of the corresponding peak in chromatogram obtained with reference solution (c) (0.2 per cent), the area of any peak corresponding to clotrimazole impurity F is not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.1 per cent), the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent) and the sum of the areas of all the secondary peaks is not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent). Ignore any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Assay. Change **to:**

Assay. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve 50 mg of the substance under examination in *methanol* and dilute to 100.0 ml with *methanol.*

Reference solution (a). A 0.05 per cent w/v solution of *clotrimazole IPRS* in *methanol*.

Reference solution (b). A solution containing 0.01 per cent w/v, each of, *clotrimazole IPRS* and *clotrimazole impurity A IPRS* in *methanol.*

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm),
- mobile phase: a mixture of 10 volumes of 0.44 per cent w/v solution of *dibasic potassium phosphate* and 30 volumes of *acetonitrile,*
-flow rate: 1.5 ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 25 µl.

The relative retention time with reference to clotrimazole for clotrimazole related compound A is about 1.2.

Inject reference solution (a) and (b). The test is not valid unless the resolution between the peaks due to clotrimazole and clotrimazole impurity A is not less than 2.0 in the chromatogram obtained with reference solution (b) and the relative standard deviation for replicate injections is not more than 2.0 per cent in the chromatogram obtained with reference solution (a).

Inject reference solution (a) and the test solution.

Calculate the content of $C_{22}H_{17}ClN_2$.

Clotrimazole Lotion. Page 1938

Assay. *Test solution*, line 1and 2
Change **from**: Transfer the equivalent of 10 mg of Clotrimazole from freshly mixed lotion
to: Weigh and transfer a quantity of the freshly mixed lotion containing equivalent to 10 mg of Clotrimazole

Last line
Change **from**: Calculate the content of $C_{22}H_{17}ClN_2$ in the lotion.
to: Determine the weight per ml of the lotion (2.4.29) and calculate the content of $C_{22}H_{17}ClN_2$, weight in volume.

Copovidone. Page 5161

Nitrogen. Para 2, line 13 and 14
Change **from**: *0.05 M sulphuric acid*
to: *0.025 M sulphuric acid*

Cyclobenzaprine Tablets. Page 5166

Related substances. Last para, line 3-6
Change **from**: The area of any peak corresponding to cyclobenzaprine *N*-oxide is not more than 1.33 times the area of the principal peak in the chromatogram obtained with the reference solution (0.2 per cent),
to: The area of any peak corresponding to cyclobenzaprine *N*-oxide is not more than 3.33 times the area of the principal peak in the chromatogram obtained with the reference solution (0.5 per cent),

Cyproheptadine Hydrochloride. Page 1989

Para 2
Change **to**: Cyproheptadine Hydrochloride contains not less than 98.0 per cent and not more than 102.0 per cent of $C_{21}H_{21}N.HC1$, calculated on the dried basis.

Assay. Change **to**:
Assay. Determine by liquid chromatography (2.4.14).

Solvent mixture. 38 volumes of *acetonitrile* and 62 volumes of *water.*

Test solution. Dissolve 40 mg of the substance under examination in the solvent mixture with the aid of ultrasound and dilute to 100.0 ml with the solvent mixture. Dilute 1.0 ml of the solution to 10.0 ml with the solvent mixture.

Reference solution. A 0.004 per cent w/v solution of *cyproheptadine hydrochloride IPRS* in the solvent mixture.

Chromatographic system
- a stainless steel column 15 cm x 4.6 mm, packed with end capped covalently modified with alkylamide groups bonded to porous silica (2.7 µm) (Such as Ascentis Express RP-Amide),
- mobile phase: A. a mixture of 62 volumes of 0.1 per cent v/v solution of *trifluoroacetic acid* in *water* and 38 volumes of *acetonitrile*,
  B. *acetonitrile*,
- a gradient programme using the conditions given below,
- flow rate: 1 ml per minute,
- spectrophotometer set at 266 nm,
- injection volume: 15 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	100	0
6.0	100	0
6.1	15	85
9.0	15	85
9.1	100	0
12.0	100	0

Inject the reference solution. The test is not valid unless the tailing factor is not more than 2.0 and the relative standard deviation for replicate injections is not more than 1.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{21}H_{21}N.HCl$.

Cyproheptadine Syrup. Page 1990

Identification

Change **to**: In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to peak in the chromatogram obtained with the reference solution.

Insert at the end.

Labelling. The label states the strength in terms of equivalent amount of anhydrous cyproheptadine hydrochloride.

Cyproheptadine Tablets. Page 1991

Insert at the end.

Storage. Store protected from light and moisture.

Labelling. The label states the strength in terms of equivalent amount of anhydrous cyproheptadine hydrochloride.

Dicyclomine Tablets. Page 2092

Identification

Change **to**: A. Transfer a quantity of the powdered tablets containing 0.1 g of Dicyclomine Hydrochloride to a separating funnel, add 10 ml of *water* and 1 ml of *hydrochloric acid.* Extract the aqueous layer with 30 ml of *chloroform,* wash the extract with two quantities, each of 20 ml, of *water* and 1 ml of 10 per cent w/v *sodium hydroxide*. Filter the chloroform solution through *anhydrous sodium sulphate.* Add 3 ml of a freshly prepared 5 per cent w/v solution of *acetyl chloride* in *anhydrous methanol*(prepared by adding acetyl chloride dropwise to *anhydrous methanol* with stirring). Evaporate under reduced pressure at room temperature until the residue has been thoroughly dried.

On the residue, determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *dicyclomine hydrochloride IPRS* treated in the same manner or with the reference spectrum of dicyclomine hydrochloride.

B. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with the reference solution.

Limit of Dicyclomine related compound A.
Reference solution (a). Line 2
Change **from**: ([1,12-Bi (cyclohexane)]-1-carboxylic acid)
to: ([1,1'-Bi (cyclohexane)]-1-carboxylic acid)

Dithranol Ointment. Page 2143

Dihydroxyanthracene. Delete the requirement.

Dihydroxyanthraquinone. Delete the requirement.

Insert before **Other tests**
Impurity B and C. Not more than 10.0 per cent of the stated amount of dithranol, calculated as the sum of the dithranol impurity B and dithranol impurity C.

Determine by liquid chromatography (2.4.14).

Test solution. Disperse a quantity of the ointment containing 20 mg of the Dithranol in 20 ml of *dichloromethane*, add 1 ml of *glacial acetic acid* and dilute to 100.0 ml with *hexane* and filter through a fine glass microfibre filter paper (Whatman GF/C).

Reference solution. Add 1.0 ml of *glacial acetic acid* to 20.0 ml of a solution containing 0.005 per cent w/v, each of, *dithranol impurity B IPRS(dantron)* and *dithranol impurity C IPRS(4,4',5,5'-tetrahydroxy-9,9'-bianthracenyl-10,10'(9H,9'H)dione)* in *dichloromethane* and dilute to 100.0 ml with *hexane*.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with porous silica particles (5 µm) (Such as Lichrosorb Si 60),
- mobile phase: a mixture of 1 volume of *glacial acetic acid*, 5 volumes of *dichloromethane* and 82 volumes of *hexane*,
- flow rate: 2 ml per minute,
- spectrophotometer set at 380 nm,
- injection volume: 20 µl.

The elution order of the peaks is dithranol impurity B and dithranol impurity C.

Inject the reference solution and the test solution.

Calculate the content of dithranol impurity B and dithranol impurity C.

Impurity D. Determine by liquid chromatography (2.4.14).

NOTE — Prepare the solutions immediately before use and protect from light.

Test solution. Disperse a quantity of the ointment containing 10 mg of the Dithranol in 25 ml of *chloroform*, evaporate under reduced pressure to a volume of about 2 ml, add 25 ml of warm *methanol*, shake, cool in ice for 15 minutes and filter. Evaporate the filtrate to dryness under reduced pressure and dissolve the residue in 10 ml of a mixture of 5 volumes of *glacial acetic acid* and 95 volumes of *acetonitrile*, filter.

Reference solution (a). Dissolve 25 mg of *dithranol impurity D IPRS(1-hydroxyanthracen-9(10H)-one)* in 0.5 ml of *glacial acetic acid* and dilute to 50.0 ml with *acetonitrile.*

Reference solution (b). Dilute 1.0 ml of reference solution (a) to 20.0 ml with *acetonitrile.*

Chromatographic system
- a stainless steel column 20 cm x 4.6 mm, packed with end-capped octadecylsilane bonded to porous silica (5 µm) (Such as Nucleosil C18),
- mobile phase: a mixture of 2.5 volumes of *glacial acetic acid*, 40 volumes of *tetrahydrofuran* and 60 volumes of *water*,
- flow rate: 1.5 ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 20 µl.

Inject reference solution (b). The test is not valid unless the relative standard deviation for replicate injections is not less than 5.0 per cent.

Inject reference solution (b) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to dithranol impurity D is not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (2.5 per cent).

Docetaxel Anhydrous. Page 2150

Assay. Insert after para 1

"Inject reference solution (a). The test is not valid unless the column efficiency is not less than 2000 theoretical plates, tailing factor is not more than 2.0 and the relative standard deviation for replicate injections is not more than 2.0 per cent."

Heavy metals

Change **to**: **Heavy metals** (2.3.13). 1.0 g complies with the limit test for heavy metals, Method B (20ppm).

Docetaxel Trihydrate. Page 2151

Sulphated ash

Change**from**:0.2 per cent.

to:0.1 per cent.

Docusate Tablets. Page 2155

Disintegration

Change **to**: **Disintegration** (2.5.1).Not more than 60 minutes, using *artificial gastric juice* in place of *water*.

Assay. After chromatographic system, para 2

Change **to**: Inject reference solution (a) and (b). The test is not valid unless the resolution between the peaks due to methylparaben and docusate is not less than 2.0 in the chromatogram obtained with reference solution (b), the tailing factor is not more than 2.5 and the relative standard deviation for replicate injections is not more than 1.8 per cent in the chromatogram obtained with reference solution (a).

Dolutegravir Tablets. Page 2157

Related substances. *Reference solution (c)*

Change **from**: A 0.001 per cent w/v solution of *dolutegravir sodium IPRS* in the solvent mixture.

to: A solution of *dolutegravir sodium IPRS* containing 0.001 per cent w/v of dolutegravir in the solvent mixture.

Doxepin Hydrochloride. Page 2182

Identification

Insert before para 1

Tests B and C may be omitted if tests A and D are carried out. Test A may be omitted if tests B, C and D are carried out.

B. Last line

Change **from**: 0.60.

to: 0.53.

Doxepin Capsules. Page 2183

Identification

Insert before para 1

Tests B and C may be omitted if tests A and D are carried out. Test A may be omitted if tests B, C and D are carried out.

B. Last line

Change **from**: 0.60.

to: 0.53.

Duloxetine Hydrochloride. Page 2198

Related substances. *Reference solution (b)*
Change **to**: *Reference solution (b).* Dissolve 20 mg of *duloxetine for system suitability IPRS (containing impurity F)* in the mobile phase and dilute to 200.0 ml with the mobile phase. In order to prepare impurity C and D, *in situ*, heat the solution at 60° for 1 hour (Solution containing impurities C, D and F).

After chromatographic system, para 1, line 3
Change **from**: and peak to valley ratio is not less than 4.0.
to: and peak-to-valley ratio (H_p/H_v) is not less than 4.0, where H_p is the height above the baseline of the peak due to duloxetine impurity F and H_v is the height above the baseline of the lowest point of the curve separating the peak due to duloxetine impurity F from the peak due to duloxetine.

Enantiomeric purity
After chromatographic system, para 2
Change **from**: Inject reference solution (b). The test is not valid unless the resolution between the peaks due to duloxetine and duloxetine impurity A is not less than 3.5.
to: Inject reference solution (a) and (b). The test is not valid unless the resolution between the peaks due to duloxetine and duloxetine impurity A is not less than 3.5inthe chromatogram obtained with reference solution (b) and the signal-to-noise ratio is not less 10 in the chromatogram obtained with reference solution (a).

Dutasteride. Page 2200
Water
Change **to**: **Water** (2.3.43). Not more than 0.5 per cent for the anhydrous form performed by heating in a tube at 180° for 4 minutes in a stream of dry inert gas and not more than 2.0 per cent for the hydrate form, determined on 0.1 g.

Escitalopram Oxalate. Page 2266
Specific optical rotation. Delete the requirement.

Enantiomeric purity. Line 1
Change **from**: 2.0 per cent
to: 3.0 per cent

Reference solution
Change **to**: *Reference solution*. Dissolve 25 mg, each of, *R-citalopram oxalate IPRS and escitalopram oxalate IPRS* in 2.5 ml of *methanol* and dilute to 50.0 ml with the mobile phase.

After chromatographic system, line 5 and 6
Change **to**: Inject the test solution and calculate the content of R- isomer by area normalisation.

Water. Line 2
Change **from**: 0.1 g.
to: 0.5 g.

Esomeprazole Gastro-resistant Capsules. Page 2274
Related substances. *Solvent mixture*, line 2 and 3
Change **from**: *disodium hydrogen orthophosphate*
to: *disodium hydrogen orthophosphate, heptahydrate*

Buffer solution
Change **from**: *Buffer solution.* Mix 5.2 ml of *1.0 M disodium hydrogen orthophosphate* buffer and 63.0 ml of *0.5 M sodium dihydrogen orthophosphate* buffer diluted to 1000.0 ml with *water*, adjusted to pH 7.6 with *0.1 M sodium hydroxide solution*.
to: *Buffer solution.* Mix 5.2 ml of *1 M sodium dihydrogen orthophosphate, monohydrate* and 63 ml of *0.5 M disodium hydrogen orthophosphate, heptahydrate* and dilute to 1000 ml with *water*, adjusted to pH 7.6.

Reference solution, line 2
Change **from**: *omeprazole sulphone IPRS* (omeprazole impurity A)

to: *omeprazole sulphone IPRS*

After chromatographic system, line 5, 7 and 8
Change **from**: omeprazole impurity A
to: omeprazole sulphone

Enantiomeric purity
Insert before *Solvent mixture*
Buffer solution. Dissolve 26.6 g of *disodium hydrogen orthophosphate, dihydrate* and 55.2 g *sodium dihydrogen orthophosphate, monohydrate* in 850 ml of *water*, adjusted to pH 6.0 and dilute to 1000 ml with *water*.

Solvent mixture, line 2
Change **from**: *disodium hydrogen phosphate*
to: *disodium hydrogen orthophosphate, heptahydrate*

Chromatographic system, mobile phase
Change **from**: a mixture of 150 ml of *acetonitrile* and 85 ml of buffer solution prepared by dissolving 26.6 g of *disodium hydrogen orthophosphate* and 55.2 g *sodium dihydrogen orthophosphate* in 1000 ml *water*, adjusted to pH 6.0 and finally diluted to 1000 ml with *water*,
to: a mixture of 150 ml of *acetonitrile* and 85 ml of buffer solution, diluted to 1000 ml with *water*,

Assay. *Solvent mixture*, line 2
Change **from**: *di-sodium hydrogen phosphate*
to: *disodium hydrogen orthophosphate, heptahydrate*

Esomeprazole Gastro-resistant Tablets. Page 2276 and 5179

Dissolution. B
Test solution
Change **to**: *Test solution*. To 5.0 ml of the filtrate, add immediately 1.0 ml of *0.25 M sodium hydroxide*.

Reference solution
Change **to**: *Reference solution.* A 0.023 per cent w/v solution of *esomeprazole magnesium IPRS* in *methanol.* Dilute a suitable volume of the solution with the dissolution medium to obtain a solution having a known concentration similar to the expected concentration of the test solution. To 5.0 ml of the solution, add immediately 1.0 ml of *0.25 M sodium hydroxide*.

Related substances. *Solvent mixture*, line 2 and 3
Change **from**: *disodium hydrogen orthophosphate*
to: *disodium hydrogen orthophosphate, heptahydrate*

Buffer solution
Change **from**: *Buffer solution.* Mix 5.2 ml of *1 M disodium hydrogen orthophosphate* and 63 ml of *0.5 M sodium dihydrogen orthophosphate* and dilute to 1000 ml with *water*, adjusted to pH 7.6 with *0.1 M sodium hydroxide solution.*
to: *Buffer solution.* Mix 5.2 ml of *1 M sodium dihydrogen orthophosphate, monohydrate* and 63 ml of *0.5 M disodium hydrogen orthophosphate, heptahydrate* and dilute to 1000 ml with *water*, adjusted to pH 7.6.

After chromatographic system, RRT table
Insert at the end
(omeprazole sulphone).

Enantiomeric purity. *Buffer solution*
Change **from**: *Buffer solution.* Dissolve 26.6 g of *disodium hydrogen orthophosphate*, 55.2 g of *sodium dihydrogen orthophosphate* in 1000 ml of *water* and adjusted to pH 6.0 with *0.1 M sodium hydroxide.*
to: *Buffer solution.* Dissolve 26.6 g of *disodium hydrogen orthophosphate, dihydrate* and 55.2 g of *sodium dihydrogen orthophosphate, monohydrate* in 1000 ml of *water,* adjusted to pH 6.0.

Solvent mixture, line 2 and 3

Change **from**: *disodium hydrogen orthophosphate*
to: *disodium hydrogen orthophosphate, heptahydrate*

Chromatographic system, mobile phase
Change **from**: a mixture of 85 volumes of buffer solution and 15 volumes of *acetonitrile,*
to: a mixture of 150 ml of *acetonitrile* and 85 ml of buffer solution, diluted to 1000 ml with *water*,

Ethanolamine. Page 2289

Identification
Change **to**: *Test A may be omitted if tests B and C are carried out. Tests B and C may be omitted if test A is carried out.*
A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *ethanolamine IPRS* or with the reference spectrum of ethanolamine.

B. Refractive index (see Tests).

C. Weight per ml(see Tests).

Anaesthetic Ether. Page 2290

Insert before **Tests**
Identification
A. Relative density (see Tests).
B. Boiling range (see Tests).

Ethinyloestradiol Tablets. Page 2292

Insert before **Uniformity of content**
Dissolution (2.5.2). *NOTE- Care must be taken not to expose any of the solutions to plastic or rubber. Fluorescent material will leach into the solutions and interfere with the quantitation of ethinyloestradiol. Also, adsorption may occur*.
Apparatus No. 2 (Paddle),
Medium.500 ml of a 0.3 per cent w/v solution of *sodium lauryl sulphate* in *water*,
Speed and time. 100 rpm and 30 minutes.

Withdraw a suitable volume of the medium and filter.

Determine by liquid chromatography (2.4.14).

Test solution. Centrifuge the filtrate at 2000 rpm for 10 minutes. Use the supernatant.

Reference solution. A 0.0025 per cent w/v solution of *ethinyloestradiol IPRS* in *methanol*. Dilute a suitable volume of the solution with the dissolution medium to obtain a solution having concentration similar to expected concentration of the test solution (*Note- Add 1 or 2 drops of methanol to dissipate the bubbles, if necessary*).

Chromatographic system
– a stainless steel column 15 cm x 4.6 mm, packed with phenyl groups bonded to porous silica (5 µm) with a guard column 1.25 cm x 4.6 mm packed with phenyl group bonded to porous silica (5 µm),
– mobile phase: a mixture of 50 volumes of a buffer solution prepared by dissolving 2.7 g of *potassium dihydrogen phosphate* in 1000 ml of *water*, adjusted to pH 6.0 with *1 M sodium hydroxide* and 50 volumes of *acetonitrile*,
– flow rate: 2 ml per minute,
– detector spectrofluorometer,
– excitation wavelength: 285 nm and emission wavelength: 310 nm,
– injection volume: 200 µl.

Inject the reference solution. The test is not valid unless the relative standard deviation for replicate injection is not more than 3.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{20}H_{24}O_2$ in the medium.

Q. Not less than 80 per cent of the stated amount of $C_{20}H_{24}O_2$.

Ethosuximide Capsules. Page 2296

Identification

Insert at the end

C. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with reference solution (a).

Insert before **Other tests**

Dissolution (2.5.2).
Apparatus No. 1 (Basket),
Medium. 900 ml of *phosphate buffer pH 6.8*,
Speed and time. 50 rpm and 30 minutes.

Withdraw a suitable volume of the medium and filter.

Determine by liquid chromatography (2.4.14).

Test solution. Use the filtrate, dilute if necessary, with the dissolution medium.

Reference solution. A 0.028 per cent w/v solution of *ethosuximide IPRS* in the dissolution medium.

Chromatographic system
– a stainless steel column 30 cm × 4.0 mm, packed with octadecylsilane bonded to porous silica (5 µm),
– mobile phase: a mixture of 80 volumes of *water* and 20 volumes of *acetonitrile*,
– flow rate: 1.5 ml per minute,
– spectrophotometer set at 254 nm,
– injection volume: 50 µl.

Inject the reference solution. The test is not valid unless the relative standard deviation for replicate injections is not more than 2.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_7H_{11}NO_2$ in the medium.

Q. Not less than 80 per cent of the stated amount of $C_7H_{11}NO_2$.

Limit of 2-Ethyl-2-Methylsuccinic Acid. Determine by liquid chromatography (2.4.14).
Test solution. Disperse a quantity of the mixed contents of the capsules containing 0.5 g of ethosuximide in the mobile phase, and dilute to 200.0 ml with the mobile phase.

Reference solution (a). A 0.0026 per cent w/v solution of *2-ethyl-2-methylsuccinic acid IPRS* in the mobile phase.

Reference solution (b). A solution containing 0.0062 per cent w/v of *ethosuximide IPRS* and 0.0064 per cent w/v of *2-ethyl-2-methylsuccinic acid IPRS* in the mobile phase.

Chromatographic system
– a stainless steel column 15 cm x 3.9 mm, packed with octadecylsilane bonded to porous silica (4 µm) (Such as Novapack C18),
– mobile phase: a mixture of 125 volumes of *acetonitrile*, 875 volumes of *water* and 1 volume of *glacial acetic acid*,
– flow rate: 1 ml per minute,
– spectrophotometer set at 225 nm,
– injection volume: 10 µl.

The relative retention time with reference to ethosuximide, for 2-ethyl-2-methylsuccinic acid is about 1.3.

Inject reference solution (b). The test is not valid unless the resolution between the peaks due to ethosuximide and 2-ethyl-2-methylsuccinic acid is not less than 3.5, the tailing factor is not more than 1.5 and the relative standard deviation for replicate injections is not more than 1.0 per cent, for ethosuximide and 5.0 per cent for 2- ethyl-2-methylsuccinic acid peak.

Inject reference solution (a) and the test solution. Run the chromatogram twice the retention time of the principal peak. In the chromatogram obtained with the test solution, the area of any peak corresponding to 2-ethyl-2-methylsuccinic acid is not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent).

Assay
Change **to**: **Assay**. Determine by liquid chromatography (2.4.14).

Test solution. Weigh and mix contents of 20 capsules. Disperse a quantity of the mixed contents containing 0.5 g of Ethosuximide in the mobile phase and dilute to 200.0 ml with the mobile phase. Dilute to 5.0 ml of the solution to 200.0 ml with the mobile phase.

Reference solution (a). A 0.0062 per cent w/v solution of *ethosuximide IPRS* in the mobile phase.

Reference solution (b). A solution containing 0.0062 per cent w/v of *ethosuximide IPRS* and 0.0064 per cent w/v of *2-ethyl-2-methylsuccinic acid IPRS* in the mobile phase.

Use the chromatographic system as described under Limit of 2-Ethyl-2-Methylsuccinic Acid.

Inject reference solution (b). The test is not valid unless the resolution between the peaks due to ethosuximide and 2-ethyl-2-methylsuccinic acid is not less than 3.5, the tailing factor is not more than 1.5 and the relative standard deviation for replicate injections is not more than 1.0 per cent, for ethosuximide and 5.0 per cent, for 2-ethyl-2-methylsuccinic acid peak.

Inject reference solution (a) and the test solution.

Calculate the content of $C_7H_{11}NO_2$ in the capsules.

Fenofibrate Capsules. Page 2343

Identification. A
Change **to:** A. Shake a quantity of the mixed contents of the capsules containing 50 mg of Fenofibrate with 10 ml of *dichloromethane* and shake vigorously. Filter through a suitable filter into a separating funnel, wash with *water* and collect the dichloromethane layer. Evaporate under a stream of nitrogen and dry under vacuum at 60° for l hour. On the residue, determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *fenofibrate IPRS* or with the reference spectrum of fenofibrate.

Finasteride. Page 2356

Insert before **Loss on drying**
Sulphated ash (2.3.18). Not more than 0.1 per cent.

Fluconazole. Page 2364

Para 2
Change **to**: Fluconazole contains not less than 98.0 per cent and not more than 102.0 per cent of $C_{13}H_{12}F_2N_6O$, calculated on the dried basis.

Identification. B
Change **to**: B. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to peak in the chromatogram obtained with the reference solution.

Related substances. Change **to**:
Related substances. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve 0.3 g of the substance under examination in the mobile phase and dilute to 100.0 ml with the mobile phase.

Reference solution. A solution containing 0.01 per cent w/v, each of, *fluconazole IPRS, fluconazole impurity A IPRS, fluconazole impurity B IPRS* and *fluconazole impurity C IPRS,* in *acetonitrile.* Dilute 1.0 ml of the solution to 10.0 ml with the mobile phase.

Chromatographic system
- a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (3.5 µm),
- column temperature. 40°,
- mobile phase: a mixture of 80 volumes of *water* and 20 volumes of *acetonitrile,*
- flow rate: 0.5 ml per minute,
- spectrophotometer set at 260 nm,
- injection volume: 20 µl.

Name	Relative retention time
Fluconazole impurity A[1]	0.5
Specified impurity[2]	0.6
Fluconazole impurity B[3]	0.81
Fluconazole impurity C[4]	0.86
Fluconazole	1.0

[1]2-[2-Fluoro-4-(1H-1,2,4-triazol-1-yl)phenyl]-1,3-bis(1H-1,2,4-triazol-1-yl)-propan-2-ol.
[2]unknown structure.
[3]2-(4-Fluorophenyl)-1,3-di(1H-1,2,4-triazol-1-yl)-propan-2-ol.
[4]1,1′-(1,3-Phenylene)di(1H-1,2,4-triazole).

Inject the reference solution. The test is not valid unless the resolution between the peaks due to fluconazole impurity B and fluconazole impurity C isnot less than 1.5 and the relative standard deviation for each peak is not more than 5.0 per cent.

Inject the reference solution and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to fluconazole impurity A and fluconazole impurity C, each of, is not more than 0.6 times the area of the corresponding peak in the chromatogram obtained with the reference solution (0.2 per cent), the area of any peak corresponding to fluconazole impurity B is not more than 0.3 times the area of the corresponding peak in the chromatogram obtained with the reference solution (0.1 per cent), the area of any peak corresponding to specified impurity at relative retention time about 0.6 is not more than 3 times the area of the principal peak in the chromatogram obtained with the reference solution (1.0 per cent), the area of any other secondary peak is not more than 0.3 times the area of the principal peak in the chromatogram obtained with the reference solution (0.1 per cent) and the sum of the areas of all the other (unknown) secondary peaks is not more than 0.9 times the area of the principal peak in the chromatogram obtained with the reference solution (0.3 per cent), and the sum of the areas of all the secondary peaks is not more than 4.5 times the area of the principal peak in the chromatogram obtained with the reference solution (1.5 per cent).

Assay. Change **to**:
Assay. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve 50 mg of the substance under examination in the mobile phase and dilute to 100.0 ml with the mobile phase.

Reference solution. A 0.05 per cent w/v solution of *fluconazole IPRS* in the mobile phase.

Use the chromatographic system as described under Related substances.

Inject the reference solution. The test is not valid unless the tailing factor is not more than 2.0 and the relative standard deviation for replicate injections is not more than 2.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{13}H_{12}F_2N_6O$.

Fluconazole Capsules. Page 2365

Related substances. Change **to**:
Related substances. Determine by liquid chromatography (2.4.14).

Test solution. Disperse a quantity of the mixed content of the capsules containing 0.3 g of Fluconazole in mobile phase A, with the aid of ultrasound for 30 minutes with occasional swirling and dilute to 100.0 ml with mobile phase A, filter.

Reference solution (a). A 0.001 per cent w/v solution of *fluconazole IPRS* in mobile phase A.

Reference solution (b). A solution containing 0.001 per cent w/v of *fluconazole IPRS* and0.0006 per cent w/v, each of, *fluconazole impurity A IPRS, fluconazole impurity B IPRS* and *fluconazole impurity C IPRS,* in mobile phase A.

Chromatographic system
- a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (3.5 µm),
- mobile phase: A. a mixture of 85 volumes of *water* and 15 volumes of *acetonitrile,*
  B. *acetonitrile,*
- flow rate: 1 ml per minute,
-a gradient programme using the conditions given below,
- spectrophotometer set at 260 nm,

- injection volume: 25 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	100	0
16	100	0
50	90	10
55	100	0
65	100	0

Name	Relative retention time
Fluconazole impurity A[1*]	0.43
Fluconazole impurity B[2*]	0.72
Fluconazole impurity C[3*]	0.83
Fluconazole	1.0

*Process impurity included for identification only and not to be included in total degradation product.
[1]2-[2-Fluoro-4-(1H-1,2,4-triazol-1-yl)phenyl]-1,3-bis(1H-1,2,4-triazol-1-yl)-propan-2-ol.
[2]2-(4-Fluorophenyl)-1,3-di(1H-1,2,4-triazol-1-yl)-propan-2-ol.
[3]1,1′-(1,3-Phenylene)di(1H-1,2,4-triazole).

Inject reference solution (b) to identify the peaks due to fluconazole impurity A, B and C.

Inject reference solution (a). The test is not valid unless the relative standard deviation for replicate injections is not more than 5.0 per cent.

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of any secondary peak is not more than 0.6 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent) and the sum of areas of all the secondary peaks is not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent). Ignore any peak with an area less than 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent).

Fluconazole Oral Suspension. Page 2366

Insert before **Usual strengths**
When stored at the temperature and for the period stated on the label during which the constituted suspension may be expected to be satisfactory for use, it contains not less than 80.0 per cent of the stated amount of fluconazole, $C_{13}H_{12}F_2N_6O$.

Insert at the end
Labelling. The label states the temperature of the storage and the period during which the constituted suspension may be expected to be satisfactory for use.

Fluconazole Tablets. Page 2368

Related substances. Change **to**:
Related substances. Determine by liquid chromatography (2.4.14).

Test solution. Disperse a quantity of the powdered tablets containing 0.3 g of Fluconazole in mobile phase A, with the aid of ultrasound for 30 minutes with occasional swirling and dilute to 100.0 ml with mobile phase A, filter.

Reference solution (a). A 0.001 per cent w/v solution of *fluconazole IPRS* in mobile phase A.

Reference solution (b). A solution containing 0.001 per cent w/v of *fluconazole IPRS* and0.0006 per cent w/v, each of, *fluconazole impurity A IPRS, fluconazole impurity B IPRS* and *fluconazole impurity C IPRS,* in mobile phase A.

Chromatographic system
- a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (3.5 µm),
- mobile phase: A. a mixture of 85 volumes of *water* and 15 volumes of *acetonitrile,*
  B. *acetonitrile,*
- flow rate: 1 ml per minute,
-a gradient programme using the conditions given below,
- spectrophotometer set at 260 nm,

- injection volume: 25 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	100	0
16	100	0
50	90	10
55	100	0
65	100	0

Name	Relative retention time
Fluconazole impurity A[1*]	0.43
Fluconazole impurity B[2*]	0.72
Fluconazole impurity C[3*]	0.83
Fluconazole	1.0

*Process impurity included for identification only and not to be included in total degradation product.
[1]2-[2-Fluoro-4-(1H-1,2,4-triazol-1-yl)phenyl]-1,3-bis(1H-1,2,4-triazol-1-yl)-propan-2-ol.
[2]2-(4-Fluorophenyl)-1,3-di(1H-1,2,4-triazol-1-yl)-propan-2-ol.
[3]1,1′-(1,3-Phenylene)di(1H-1,2,4-triazole).

Inject reference solution (b) to identify the peaks due to fluconazole impurity A, B and C.

Inject reference solution (a). The test is not valid unless the relative standard deviation for replicate injections is not more than 5.0 per cent.

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of any secondary peak is not more than 0.6 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent) and the sum of areas of all the secondary peaks is not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent). Ignore any peak with an area less than 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent).

Fluocinolone Acetonide. Page 2382

Line 1
Change **from**: $C_{24}H_{30}F_2O_6$ Mol. Wt. 452.5
to: $C_{24}H_{30}F_2O_6$ Mol. Wt. 452.5 (anhydrous)
$C_{24}H_{34}F_2O_8$ Mol. Wt. 488.5 (dihydrate)

Loss on drying
Change **to**: **Loss on drying** (2.4.19). Not more than 1.0 per cent for anhydrous form and between 7.0 per cent to 8.5 per cent for dihydrate form, determined on 1.0 g by drying in an oven at 105° for 3 hours.

Fluphenazine Decanoate. Page 2399

Insert after **Identification**
Tests B and D may be omitted if tests A and C are carried out. Tests A and D may be omitted if tests B and C are carried out.

Frusemide. Page 2433

Para 2
Change **to:** Frusemide contains not less than 98.0 per cent and not more than 102.0 per cent of $C_{12}H_{11}ClN_2O_5S$, calculated on the dried basis.

Identification. C
Change **to**: C. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to peak in the chromatogram obtained with reference solution (a).

Related substances. Change **to**:
Related substances. Determine by liquid chromatography (2.4.14).

NOTE- Protect the solutions from light.

Solvent mixture. 97.8 volumes of a mixture of equal volumes of *acetonitrile* and *water* and 2.2 volumes of *glacial acetic acid.*

Test solution. Dissolve 50 mg of the substance under examination in the solvent mixture and dilute to 50.0 ml with the solvent mixture.

Reference solution (a). A solution containing 0.005 per cent w/v, each of, *frusemide related compound A IPRS* and *frusemide related compound B IPRS,* in the solvent mixture. Dilute 1.0 ml of the solution to 10.0 ml with the solvent mixture.

Reference solution (b). A solution containing 0.002 per cent w/v of *frusemide IPRS* and 0.0012 per cent w/v of *frusemide related compound A IPRS* in the solvent mixture.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (Such as Spherisorb ODS),
- mobile phase: a mixture of 30 volumes of *tetrahydrofuran,* 70 volumes of *water* and 1 volume of *glacial acetic acid,*
- flow rate: 1 ml per minute,
- spectrophotometer set at 254 nm and 272 nm,
- injection volume: 20 µl.

[NOTE- The 2,4-dichloro-5-sulfamoylbenzoic acid impurity does not respond at 272 nm, and the 2,4-bis(furfurylamino)-5-sulfamoylbenzoic acid impurity has a very intense absorbance at 254 nm. The response for frusemide is at 254 nm.]

Inject reference solution (b). The test is not valid unless the resolution between the peaks due to frusemide and frusemide related compound A is not less than 2.5 and the relative standard deviation is not more than 2.0 per cent, for frusemide peak.

Inject reference solution (a) and the test solution at 254 nm. Run the chromatogram 2.5 times the retention time of the principal peak. In the chromatogram obtained with the test solution, the sum of areas of all the secondary peaks eluting before the frusemide peak is not more than the area of the frusemide related compound B peak in the chromatogram obtained with reference solution (a) (0.5 per cent).

Inject reference solution (a) and the test solution at 272 nm. Run the chromatogram 2.5 times the retention time of the principal peak. In the chromatogram obtained with the test solution, the sum of areas of all the secondary peaks eluting after the frusemide peak is not more than the area of the frusemide related compound A peak in the chromatogram obtained with reference solution (a) (0.5 per cent).

Assay. Change **to:**
Assay. Determine by liquid chromatography (2.4.14).

NOTE- Protect the solutions from light.

Test solution. Dissolve 20 mg of the substance under examination in the solvent mixture and dilute to 100.0 ml with the solvent mixture.

Reference solution (a). A 0.02 per cent w/v solution of *frusemide IPRS* in the solvent mixture.

Reference solution (b). A solution containing 0.002 per cent w/v of *frusemide IPRS* and 0.0012 per cent w/v of *frusemide related compound A IPRS* in the solvent mixture.

Use the chromatographic system as described under Related substances with the following modification
- spectrophotometer set at 272 nm.

Inject reference solution (a) and (b). The test is not valid unless the resolution between the peaks due to frusemide and frusemide related compound A is not less than 2.5 in the chromatogram obtained with reference solution (b) and the relative standard deviation for replicate injections is not more than 2.0 per cent in the chromatogram obtained with reference solution (a).

Inject reference solution (a) and the test solution.

Calculate the content of $C_{12}H_{11}ClN_2O_5S$.

Frusemide Injection. Page 2434

Identification. A
Change **to:** A. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to peak in the chromatogram obtained with reference solution (a).

Related substances. Change **to**:
Limit of Frusemide related compound B. Determine by liquid chromatography (2.4.14).

NOTE- Protect the solutions from light.

Solvent mixture. 97.8 volumes of a mixture of equal volumes of *acetonitrile* and *water* and 2.2 volumes of *glacial acetic acid*.

Test solution. Dilute a volume of the injection containing 10 mg of Frusemide to 10.0 m1 with the solvent mixture and mix.

Reference solution (a). A 0.1 per cent w/v solution of *frusemide IPRS* in the solvent mixture.

Reference solution (b). A 0.001 per cent w/v solution of *frusemide related compound B IPRS* in the solvent mixture.

Reference solution (c). A solution containing 0.002 per cent w/v of *frusemide IPRS* and 0.0012 per cent w/v of *frusemide related compound A IPRS* in the solvent mixture.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (Such as Spherisorb ODS),
- mobile phase: a mixture of 30 volumes of *tetrahydrofuran,* 70 volumes of *water* and 1 volume of *glacial acetic acid,*
- flow rate: 1 ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 20 µl.

[NOTE—The 2,4-dichloro-5-sulfamoylbenzoic acid impurity does not respond at 272 nm, and the 2,bis(furfurylamino)-5-sulfamoylbenzoic acid impurity has a very intense absorbance at 254 nm. The response for frusemide is at 254 nm.]

Inject reference solution (c). The test is not valid unless the resolution between the peaks due to frusemide and frusemide related compound A is not less than 2.5 and the relative standard deviation for replicate injections is not more than 2.0 per cent, for frusemide peak.

Inject reference solution (b) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to frusemide related compound B is not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent).

For veterinary use

Inject reference solution (b) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to frusemide related compound B is not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (2.5 per cent).

Assay. Change **to**:
Assay. Determine by liquid chromatography (2.4.14), as described under Limit of Frusemide related compound B.

NOTE- Protect the solutions from light.

Inject reference solution (c). The test is not valid unless the resolution between the peaks due to frusemide and frusemide related compound A is not less than 2.5 and the relative standard deviation for replicate injections is not more than 2.0 per cent, for frusemide peak.

Inject reference solution (a) and the test solution.

Calculate the content of $C_{12}H_{11}ClN_2O_5S$ in the injection.

Frusemide Tablets. Page 2434

Identification. A
Change **to:** A. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with reference solution (a).

Related substances. Change **to:**
Limit of Frusemide related compound B. Determine by liquid chromatography (2.4.14).

NOTE- Protect the solutions from light.

Solvent mixture. 97.8 volumes of a mixture of equal volumes of *acetonitrile* and *water* and 2.2 volumes of *glacial acetic acid.*

Test solution. Weigh and powder 20 tablets. Disperse a quantity of the powder containing 50 mg of Frusemide, in the solvent mixture with the aid of ultrasound for 10 minutes and dilute to 50.0 ml with the solvent mixture, mix and filter.

Reference solution (a). A 0.1 per cent w/v solution of *frusemide IPRS* in the solvent mixture.

Reference solution (b). A 0.0008 per cent w/v solution of *frusemide related compound B IPRS* in the solvent mixture.

Reference solution (c). A solution containing 0.002 per cent w/v of *frusemide IPRS* and 0.0012 per cent w/v of *frusemide related compound A IPRS* in the solvent mixture.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (Such as Spherisorb ODS),
- mobile phase: a mixture of 30 volumes of *tetrahydrofuran,* 70 volumes of *water* and1 volume of *glacial acetic acid,*
- flow rate: 1 ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 20 µl.

[NOTE—The 2,4-dichloro-5-sulfamoylbenzoic acid impurity does not respond at 272 nm, and the 2,4-bis(furfurylamino)-5-sulfamoylbenzoic acid impurity has a very intense absorbance at 254 nm. The response for frusemide is at 254 nm].

Inject reference solution (c). The test is not valid unless the resolution between the peaks due to frusemide and frusemide related compound A is not less than 2.5 and the relative standard deviation for replicate injection is not more than 2.0 per cent, for frusemide peak.

Inject reference solution (b) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to frusemide related compound Bis not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.8 per cent).

Assay. Change **to:**
Assay. Determine by liquid chromatography (2.4.14), as described under Limit of Frusemide related compound B.

Inject reference solution (a) and the test solution.

Calculate the content of $C_{12}H_{11}ClN_2O_5S$ in the tablets.

Gelatin. Page 2455

Iron. Para 3
Change **to**: *Reference solution*. *Iron standard solution (8 ppm),* dilute with *water* as necessary*(Note- Prepare the solution immediately before use).*

Chromium. *Chromium standard solution (100 ppm)*
Insert at the end
(Note- Prepare the solution immediately before use).

Zinc. Para 3
Change **to**: *Reference solution*. *Zinc standard solution (10 ppm),* dilute with *water* as necessary*(Note- Prepare the solution immediately before use).*

Gemifloxacin Tablets. Page2463

Assay. *Reference solution*, line 1

Change **from**: 0.01 per cent
to: 0.012 per cent

Glimepiride. Page 2476

Impurity A. *Reference solution (a)*
Change **to:** *Reference solution (a).* Dissolve 40 mg of *glimepiride IPRS* in 20 ml of *dichloromethane* and dilute to 100.0 ml with the mobile phase. Dilute 1.0 ml of the solution to 100.0 ml with the mobile phase.

Reference solution (b)
Change **to:** *Reference solution (b).* A solution containing 0.25 per cent w/v of *glimepirideIPRS* and 0.00125 per cent w/v of *glimepiride related compound A IPRS* prepared by dissolving in minimum amount of *dichloromethane* and diluted with the mobile phase.

After chromatographic system, para 1
Change **to:** The relative retention time with reference to glimepiride for glimepiride impurity A is about 0.9.

Inject reference solution (b). The test is not valid unless the peak-to-valley ratio is not less than 2.0, where *Hp* is the height above the baseline of the peak due to glimepiride impurity A and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to glimepiride and the signal-to-noise ratio is not less than 15 for the peak due to glimepiride impurity A.

Glyceryl Trinitrate Tablets. Page 2489

Change **to**: **Glyceryl Trinitrate Sublingual Tablets**

Para 1, line 1
Change **from**: Glyceryl Trinitrate Tablets
to: Glyceryl Trinitrate Sublingual Tablets

Other tests
Change **from**: Comply with the tests stated under Tablets. The test for Disintegration does not apply.
To: Comply with the tests stated under Tablets.

Labelling
Change **to**: The labeling indicates that the Sublingual Tablets are for sublingual use, and the label directs that the Sublingual Tablets be dispensed in the original, un-opened container, labeled with the following statement directed to the patient. "Warning: To prevent loss of potency, keep these tablets in the original container or in a supplemental glyceryl trinitrate container specifically labeled as being suitable for Glyceryl Trinitrate Sublingual Tablets. Close tightly immediately after each use."

Homatropine Methylbromide. Page 2520

Identification
Change **to**: **Identification**
A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *homatropine methylbromide IPRS* or with the reference spectrum of homatropine methylbromide.

B. It gives reaction (A) of bromides (2.3.1).

Related substances. Chromatographic system, mobile phase A, line 3
Change **from**: *sodium heptanesulphonate monohydrate*
to: *sodium pentanesulphonate monohydrate*

Hydrochlorothiazide. Page 2527

Identification. Para 1
Change **to**: *Test A may be omitted if tests B, C and D are carried out. Tests B, C and D may be omitted if test A is carried out.*

Hydroxyprogesterone Hexanoate. Page 2546

Identification

Insert before A

Test A may be omitted if tests B, C and D are carried out. Tests B, C and D may be omitted if test A is carried out.

Hyoscine Butylbromide Injection. Page 2556

Identification

Change **to**: A. Evaporate to dryness a volume of the injection containing 0.1 g of Hyoscine Butylbromide, shake the residue with 20 ml of *chloroform*, filter, evaporate the filtrate to dryness and triturate the residue with 5 ml of *acetonitrile*. Evaporate to dryness and dry the residue at 50° at a pressure not exceeding 0.7 kPa for 1 hour. On the residue, determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *hyoscine butylbromide IPRS* or with the reference spectrum of hyoscine butylbromide.

B. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with the reference solution.

Hyoscine Butylbromide Tablets. Page 2558

Identification

Change **to**: A. Shake a quantity of the powdered tablets containing 50 mg of Hyoscine Butylbromide with 20 ml of *chloroform,* filter, evaporate the filtrate to dryness and triturate the residue with 5 ml of *acetonitrile*. Evaporate to dryness and dry the residue at 50° at a pressure not exceeding 0.7 kPa for 1 hour. On the residue, determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *hyoscine butylbromide IPRS* or with the reference spectrum of hyoscine butylbromide.

B. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with the reference solution.

Imipramine Tablets. Page 2594

Identification

Change **to**: Triturate a quantity of the powdered tablets containing about 0.1 g of Imipramine Hydrochloride with 10 ml of *chloroform*, filter, evaporate the filtrate to low bulk, add *ether* until a turbidity is produced, heat on a steam bath to produce a clear solution, cool and allow to stand. The precipitate is formed, after recrystallisation from *acetone.* Filter the crystalline precipitate, wash with ether and dry under vacuum at 105º for 30 minutes. The residue complies with the following tests.

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *imipramine hydrochloride IPRS* or with the reference spectrum of imipramine hydrochloride.

B. It gives reaction (A) of chlorides (2.3.1).

Uniformity of content. Para 2, lines 1 to 4

Change **from**: Powder one tablet, shake with 25 ml of *0.1 M hydrochloric acid* for 30 minutes, add sufficient *0.1 M hydrochloric acid* to produce 100.0 ml and filter. Dilute 10.0 ml of the filtrate to 50.0 ml with *0.1 M hydrochloric acid* and measure …

to: Disperse one intact tablet in *0.1M hydrochloric acid*, with the aid of ultrasound for 30 minutes and dilute with *0.1Mhydrochloric acid* to obtain a solution containing 0.0025 per cent w/v of Imipramineand measure …

Isoprenaline Sulphate. Page 2635

Identification. A, para 2, last line

Change **from**: isoprenaline.

to: isoprenaline sulphate.

Insert before **Sulphated ash**

Chlorides (2.3.12). Dissolve 0.7 g in 100.0 ml of *water*, 15.0 ml of resulting solution complies with the limit test for chlorides (0.14 per cent).

Ketorolac Tromethamine. Page 2671

Identification. B

Change **to**: B. In the Assay, the principal peak in the chromatogram obtained with the test solution correspond to the peak in the chromatogram obtained with reference solution (a).

Related substances. After chromatographic system, para 1 & 2
Change **to**:
Inject reference solution (a) and (c). The test is not valid unless the resolution between the peaks due to ketorolac 1-keto analog and ketorolac is not less than 1.5 in the chromatogram obtained with reference solution (c), the column efficiency is not less than 5500 theoretical plates and the relative standard deviation for replicate injections is not more than 1.5 per cent in the chromatogram obtained with reference solution (a).

Inject reference solution (b) and the test solution. Run the chromatogram three times the retention time of the principal peak. The area of any peak at relative retention time of 0.54 and 0.66, each of, is not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent), the area of any peak corresponding to ketorolac 1-hydroxy analog and ketorolac 1-keto analog, each of, is not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent), the area of any other secondary peak is not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent) and the sum of the areas of all the secondary peaks is not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent).

Levofloxacin Injection. Page 2746

Related substances. *Reference solution (a)*
Change **from**: A 0.025 per cent w/v solution of *levofloxacin IPRS* in the solvent mixture.
to: A solution of *levofloxacin hemihydrate IPRS* containing 0.025 per cent w/v of levofloxacin in the solvent mixture.

Assay. *Reference solution*
Change **from**: A 0.1 per cent w/v solution of *levofloxacin IPRS* in *0.1M hydrochloric acid*. Dilute 5.0 ml of the solution to 25.0 ml with *water*.
to: A solution of *levofloxacin hemihydrate IPRS* containing 0.1 per cent w/v of levofloxacin in *0.1M hydrochloric acid*. Dilute 5.0 ml of the solution to 25.0 ml with *water*.

Levosalbutamol Hydrochloride. Page 2753

Identification
Change **to**: A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *levosalbutamol hydrochloride IPRS* or with the reference spectrum of levosalbutamol hydrochloride.

B. It gives reaction (A) of chlorides (2.3.1).

Levosalbutamol Sulphate. Page 2756

Identification. B
Change **to**: B. It gives reaction (A) of sulphates (2.3.1).

Linezolid. Page 2766

Identification. B, last line
Change **from**: reference solution (b).
to: reference solution (c).

Specific optical rotation
Change **to**: **Enantiomeric purity.** Determine by liquid chromatography (2.4.14).

Test solution. Dissolve 50 mg of the substance under examination in *ethanol* with the aid of ultrasound and dilute to 100.0 ml with *ethanol*.

Reference solution. A solution containing 0.0025 per cent w/v, each of, *linezolid IPRS* and *linezolid R-isomer IPRS,* in *ethanol*.

Chromatographic system

- a stainless steel column 15 cm x 4.6 mm, packed with amylose tris-3,5-dimethylphenylcarbamate-coated, bonded to porous silica (5 µm) (Such as Chiralpak AD-H),
- mobile phase: a mixture of 65 volumes of *hexane*, 35 volumes of *ethanol* and0.1 volume of *trifluoroacetic acid,*
- flow rate: 1.5 ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 20 µl.

Name	Relative retention time
Linezolid R-isomer[1]	0.84
Linezolid	1.0

[1]N-{[(R)-3-(3-Fluoro-4-morpholinophenyl)-2-oxo-5-oxazolidinyl]methyl}acetamide.

Inject the reference solution. The test is not valid unless the resolution between the peaks due to linezolid and linezolid R-isomer is not less than 1.5.

Inject the test solution. Run the chromatogram 3 times the retention time of the principal peak, the area of any peak corresponding to linezolid R-isomer is not more than 0.3 per cent, calculated by area normalization.

Related substances. Change **to**:
Related substances. Determine by liquid chromatography (2.4.14).

*Solvent mixture.*65 volumes of *water* and 35 volumes of *acetonitrile.*

Test solution (a). Dissolve 80 mg of the substance under examination in the solvent mixture and dilute to 100.0 ml with the solvent mixture.

Test solution (b). Dilute 1.0 ml of test solution (a) to 10.0 ml with the solvent mixture.

Reference solution (a). A 0.008 per cent w/v solution of *linezolid IPRS* in the solvent mixture.

Reference solution (b). Dilute 1.0 ml of reference solution (a) to 100.0 ml with the solvent mixture.

Reference solution (c). A solution containing 0.005 per cent w/v, each of, *linezolid IPRS* and *linezolid related compound D IPRS* in the solvent mixture.

Chromatographic system

- a stainless steel column 7.5 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (3 µm) (Such as discovery HS C18),
- sample temperature 15º,
- mobile phase: A**.** a mixture of 80 volumes of 0.14 per cent w/v solution of *monobasic potassium phosphate*, 15 volumes of *methanol* and5 volumes of *acetonitrile,*
  B. a mixture of 50 volumes of 0.14 per cent w/v solution of *monobasic potassium phosphate* and 50 volumes of *methanol,*
- a gradient programme using the conditions given below,
- flow rate: 1.5 ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 10 µl.

Time (in min)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	80	20
8	57	43
18	0	100
25	0	100
25.1	80	20
30	80	20

Name	Relative retention time
Linezolid N- oxide[1]	0.20
Linezolid related compound C[2]	0.31
Desfluoro linezolid[3]*(if present)	0.63
Linezolid	1.0
Linezolid related compound D[4]	1.4

*If possible from the manufacturing process,
[1](*S*)-4-{4-[5-(Acetamidomethyl)-2-oxooxazolidin-3-yl]-2-fluorophenyl}morpholine 4-oxide,
[2](*S*)-5-(Aminomethyl)-3-(3-fluoro-4-morpholinophenyl)oxazolidin-2-one (linezolid amine),
[3](*S*)-*N*-{[3-(4-Morpholinophenyl)-2-oxooxazolidin-5-yl]methyl}acetamide,
[4](*R*)-[3-(3-Fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl]methylmethanesulfonate.

Inject reference solution (b) and (c). The test is not valid unless the resolution between the peaks due to linezolid and linezolid related compound D is not less than 3.0 in the chromatogram obtained with reference solution (c),the tailing factor is not more than 1.5 and the relative standard deviation for replicate injections is not more than 5.0 per cent in the chromatogram obtained with reference solution (b).

Inject reference solution (b) and test solution (a). In the chromatogram obtained with test solution (a), the area of any peak corresponding to linezolid N- oxide and desfluoro linezolid, each of, is not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent), the area of any peak corresponding to linezolid related compound C, is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent), the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent). Ignore any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Assay. Change **to**:
Assay. Determine by liquid chromatography (2.4.14), as described under Related substances with the following modifications.

Inject reference solution (a) and (c). The test is not valid unless the resolution between the peaks due to linezolid and linezolid related compound D is not less than 3.0 in the chromatogram obtained with reference solution (c),the tailing factor is not more than 1.5 and the relative standard deviation for replicate injections is not more than 1.0 per cent in the chromatogram obtained with reference solution (a).

Inject reference solution (a) and test solution (b).

Calculate the content of $C_{16}H_{20}FN_3O_4$.

Linezolid Tablets. Page 2768

Related substances. Change **to**:
Related substances. Determine by liquid chromatography (2.4.14).

Solvent mixture. 55 volumes of mobile phase A and 45 volumes of mobile phase B.

Test solution. Weigh a quantity of the powdered tablets containing 100 mg of Linezolid, add 55 ml of mobile phase A, shake for 10 minutes and sonicate for 10 minutes and dilute to 100.0 ml with *methanol*.

Reference solution(a). A 0.0002 per cent w/v solution of *linezolid IPRS* in the solvent mixture.

Reference solution(b). Dilute 2.5 ml of reference solution (a) to10.0 ml with the solvent mixture.

Reference solution(c). A solution containing 0.1 per cent w/v of *linezolid IPRS* and 0.00015 per cent w/v, each of, *linezolid related compound A IPRS* and *linezolid related compound B IPRS* in the solvent mixture.

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5µm),
- column temperature 50º,
- mobile phase: A. a 0.68 per cent w/v solution of *potassium dihydrogen phosphate* in *water*,
  B. *methanol*,
- a gradient programme using the conditions given below,
- flow rate: 1 ml per minute,
- spectrophotometer set at 251 nm,

– injection volume: 20µl.

Time (in min)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	65	35
5	65	35
35	35	65
40	65	35
50	65	35

Name	Relative retention time
Linezolid related compound C[1]	0.40
Linezolid	1.0
Linezolid related compound B[2]	1.70
Linezolid related compound A[3]	1.80

[1](*S*)-5-(Aminomethyl)-3-(3-fluoro-4-morpholinophenyl)oxazolidin-2-one,
[2](*S*)-N-{[3-(3-Fluoro-4-morpholinophenyl)-2-oxoxxazolidin-5-yl]methyl}thioacetamide,
[3](*R*)-5-(Azidomethyl)-3-(3-fluoro-4-morpholinophenyl)oxazolidin-2-one.

Inject reference solution (a), (b) and (c). The test is not valid unless the resolution between the peaks due to linezolid related compound A and linezolid related compound B is not less than 1.5 in the chromatogram obtained with reference solution (c), the tailing factor is not more than 2.0 in the chromatogram obtained with reference solution (c), the relative standard deviation for replicate injections is not more than 5.0 per cent in the chromatogram obtained with reference solution (a) and the signal-to-noise ratio is not less than 10 in the chromatogram obtained with reference solution (b).

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to linezolid related compound Cis not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent),the area of any other secondary peak is not more than 0.85 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.17 per cent) and the sum of the areas of all the secondary peaks is not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent). Ignore any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loperamide Hydrochloride. Page 2776

Identification

Change **to**: A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *loperamide hydrochloride IPRS* or with the reference spectrum of loperamide hydrochloride.

B. Dissolve 50 mg in a mixture of 0.4 ml of *strong ammonia solution* and 2 ml of *water*. Mix, allow to stand for 5 minutes and filter. Acidify the filtrate with *2 M nitric acid*. It gives reaction (A) of chlorides (2.3.1).

Loratadine Tablets. Page 2785

Insert before **Impurity H**

Dissolution (2.5.2).
Apparatus No. 2 (Paddle),
Medium. 900 ml of *0.1 M hydrochloric acid*,
Speed and time. 50 rpm and 60 minutes.

Withdraw a suitable volume of the medium and filter. Measure the absorbance of the filtrate, dilute suitably, if necessary, with the dissolution medium, at the maximum at about 280 nm (2.4.7). Calculate the content of $C_{22}H_{23}ClN_2O_2$ in the medium from the absorbance obtained from a solution of known concentration of *loratadine IPRS* in the dissolution medium.

Q. Not less than 80 per cent of the stated amount of $C_{22}H_{23}ClN_2O_2$.

Lorazepam. Page 2787

Related substances. Change **to**:

Related substances. Determine by liquid chromatography (2.4.14).

Solvent mixture. 75 volumes of *methanol* and 25 volumes of *water*.

Test solution. Dissolve 0.32 g of substance under examination in 100.0 ml of the solvent mixture.

Reference solution (a). A 0.00032 per cent w/v solution of *lorazepam IPRS* in the solvent mixture.

Reference solution (b). A solution containing 0.32 per cent w/v of *lorazepam IPRS* and 0.0032 per cent w/v, each of, *lorazepam related compound A IPRS*, *lorazepam related compound B IPRS*, *lorazepam related compound C IPRS*, *lorazepam related compound D IPRS* and *lorazepam related compound E IPRS* in the solvent mixture.

Reference solution (c). A 0.00016 per cent w/v solution of *lorazepam related compound B IPRS* in the solvent mixture. Dilute 1.0 ml of the solution to 10.0 ml with the solvent mixture.

Chromatographic system
– a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (Such as YMC-Pack ODS-A),
– column temperature: 5º,
– sample temperature: 4°,
– mobile phase: a mixture of 50 volumes of *acetonitrile*, 50 volumes of *water* and 1.2 volumes of *glacial acetic acid*,
– flow rate: 1 ml per minute,
– spectrophotometer set at 230 nm,
– injection volume: 100 µl.

Name	Relative retention time	Correction factor
Lorazepam	1.0	---
Lorazepam related compound D[1]	1.4	---
Lorazepam related compound A[2]	1.7	---
Lorazepam related compound E[3]	1.9	0.77
Lorazepam related compound C[4]	2.1	---
Lorazepam related compound B[5]	5.5	---

[1]6-chloro-4-(*O*-chlorophenyl)-2-quinazolinecarboxylic acid,
[2]7-chloro-5-(*O*-chlorophenyl)-1,3-dihydro-3-acetoxy-2*H*-1,4-benzodiazepin-2-one,
[3]6-chloro-4-(*O*-chlorophenyl)-2-quinazoline methanol,
[4]6-chloro-4-(*O*-chlorophenyl)-2-quinazolinecarboxaldehyde,
[5]2-amino-2',5-dichlorobenzophenone.

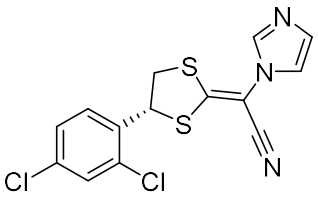
Inject reference solution (a), (b) and (c). The test is not valid unless the resolution between the peaks due to lorazepam related compound A and lorazepam related compound E is not less than 1.2 in the chromatogram obtained with reference solution (b), the relative standard deviation for replicate injections is not more than 5.0 per cent in the chromatogram obtained with reference solution (a) and the signal-to-noise ratio for lorazepam related compound B peak is not less than 10 in the chromatogram obtained with reference solution (c).

Inject reference solution (a) and the test solution. Run the chromatogram 8 times the retention time of the principal peak for the test solution. The area of any peak corresponding to lorazepam related compound D and lorazepam related compound E, each of, is not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent), the area of any peak corresponding to lorazepam related compound A is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent), the area of any peak corresponding to lorazepam related compound C is not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.30 per cent), the area of any peak corresponding to lorazepam related compound B is not more than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.01 per cent), the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent) and the sum of the areas of all the secondary peaks is not more than 7.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.75 per cent).

Luliconazole. Page 2798

Structure

Change **to**:



Para 1
Change **from**: Luliconazole is (2E)[4-(2,4-Dichlorophenyl)-1,3-dithiolan-2- ylidene](1H-imidazol-1-yl)acetonitrile.
to: Luliconazole is (2E)-[(4R)-4-(2,4-Dichlorophenyl)-1,3-dithiolan-2-ylidene](1H-imidazol-1-yl)acetonitrile.

Magnesium Stearate. Page 2817
Para 2, line 1
Change **from**: 3.8 per cent
to:4.0 per cent

Identification
Insert before para 1
Tests A and B may be omitted if tests C and D are carried out. Test C may be omitted if tests A, B and D are carried out.

Mannitol. Page 2824
Insert before **Arsenic**
Related substances. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve 0.5 g of the substance under examination in *water* and dilute to 10.0 ml with *water.*

Reference solution (a). A solution containing 2.5 per cent w/v, each of, *sorbitol IPRS* and *mannitol IPRS* in *water.*

Reference solution (b). A solution containing 0.1 per cent w/v, each of, *maltitol IPRS* and *isomalt IPRS* in *water.*

Reference solution (c). A 5.0 per cent w/v solution of *mannitol IPRS* in *water.*

Reference solution (d). Dilute 1.0 ml of reference solution (c) to 100.0 ml with *water.*

Chromatographic system
- a stainless steel column 30 cm x 7.8 mm, packed with strong cation-exchange resin consisting of sulphonated cross-linked styrene-divinylbenzene copolymer in the calcium form (9 µm) (Such as Aminex HPX-87C),
- column temperature: 85°,
- mobile phase: degassed *water*,
- flow rate: 0.5 ml per minute,
- detector temperature: 40º (maintain at a constant temperature),
- refractive index detector,
- injection volume: 20 µl.

Name	Relative retention time
Isomalt (1st peak) (Impurity C)	0.60
Maltitol (Impurity B)	0.69
Isomalt (2st peak) (Impurity C)	0.73
Mannitol (Retention time: about 20 minutes)	1.0
Sorbitol (Impurity A)	1.2

NOTE- Isomalt elutes in two peaks and Coelution of impurity B and the second peak due to impurity C may be observed.

Inject reference solution (b) to identify the peaks due to maltitol and isomalt.

Inject reference solution (a). The test is not valid unless the resolution between the peaks due to sorbitol and mannitol is not less than 2.0.

Inject reference solution (d) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to sorbitol and sum of areas of the peaks corresponding to isomalt and maltitol, each of, is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (d) (2.0 per cent), the area of any other secondary peak is not more than 0.1 times the area of the principal peak in the chromatogram obtained with reference

solution (d) (0.1 per cent) and the sum of areas of all the secondary peaks is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (d) (2.0 per cent). Ignore any peak with an area less than 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (d) (0.05 per cent).

Sorbitol. Delete the requirement

Assay. Change **to**:
Assay. Determine by liquid chromatography (2.4.14),as described under Related substances.

Inject reference solution (a). The test is not valid unless the resolution between the peaks due to sorbitol and mannitol is not less than 2.0.

Inject reference solution (c) and the test solution.

Calculate the content of $C_6H_{14}O_6$.

Mercaptopurine. Page 5212

Related substances. *Reference solution (a)*
Change **to**: *Reference solution (a)*. A 0.006 per cent w/v solution of *mercaptopurine IPRS* in solution A. *(NOTE – Use methanol equivalent to 2.5 per cent of the final volume to dissolve)*. Dilute 1.0 ml of the solution to 50.0 ml with mobile phase A.

Mesalazine. Page 2865

Chlorides. Change **to**:
Chlorides (2.3.12).Disperse 0.25 g with 40 ml of *water* with the aid of ultrasound and filter. The filtrate complies with the limit test for chlorides (0.1 per cent).

Mesalazine Prolonged-release Tablets. Page 2867

Related substances. *Test solution*
Change **to**: *Test solution*. Disperse a quantity of the powdered tablets containing 200 mg of Mesalazine in 150 ml of *0.01M hydrochloric acid,* with the aid of ultrasound for 10 minutes and dilute to 200.0 ml with *0.01 M hydrochloric acid*, filter.

Metformin Hydrochloride. Page 2874

Related substances. Change **to**:
Related substances. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve 50 mg of the substance under examination in the mobile phase and dilute to 10.0 ml with the mobile phase.

Reference solution (a). A 0.0005 per cent w/v solution of *metformin hydrochloride IPRS* inthe mobile phase.

Reference solution (b). A 0.02 per cent w/v solution of *dicyandiamide IPRS* in *water*. Dilute 1.0 ml of the solution to 200.0 ml with the mobile phase.

Reference solution (c). A solution containing 0.025 per cent w/v of *metformin hydrochloride IPRS* and 0.01 per cent w/v of *melamine (2,4,6-triamino-1,3,5-triazine) IPRS* in *water*. Dilute 1.0 ml of the solution to 50.0 ml with the mobile phase.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with strongly acidic cation-exchange resin bonded to porous silica (10 µm) (Such as Partisil SCX),
- mobile phase: a 1.7 per cent w/v solution of *ammonium dihydrogen orthophosphate*, adjusted to pH 3.0 with *orthophosphoric acid*,
- flow rate: 1.0-1.7 ml per minute,
- spectrophotometer set at 218 nm,
- injection volume: 20 µl.

Inject reference solution (c). The test is not valid unless the resolution between the peaks due to melamine and metformin hydrochloride is not less than 10.0.

Inject reference solution (a), (b) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to dicyandiamide is not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.02 per cent), the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent) and the sum of the areas of all the secondary peaks is not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent). Ignore any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Metformin Oral Solution. Page 2875

Related substances. *Reference solution (a)*
Change **to**: *Reference solution (a).* A 0.0005 per cent w/v solution of *metformin hydrochloride IPRS* in the mobile phase.

Last para. line 9
Change **from**: 4 times
to: 5 times

Line 11
Change **from**: (0.4 per cent).
to: (0.5 per cent).

Metformin Hydrochloride Prolonged-release Tablets. Page 2876 and 5216

Related substances. Change **to**:
Related substances. Determine by liquid chromatography (2.4.14), as described under Assay with the following modifications.

Test solution. Weigh and powder 20 tablets. Disperse a quantity of the powder containing 500 mg of Metformin Hydrochloride in solution A with the aid of ultrasound with intermittent shaking and dilute to 100.0 ml with solution A and filter.

Inject reference solution (c) and the test solution. In the chromatogram obtained with the test solution, the area of any secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.1 per cent) and the sum of the areas of all the secondary peaks is not more than 6 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.6 per cent). Ignore any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Assay
Insert before chromatographic system
Reference solution (c). A 0.0005 per cent w/v solution of *metformin hydrochloride IPRS* in solution A.

Insert at the end
Storage. Store protected from light and moisture, at a temperature not exceeding 30°.

Metformin Tablets. Page 2878 and 5217

Identification. C
C. Delete the requirement

Related substances. Change **to**:
Related substances. Determine by liquid chromatography (2.4.14), as described under Assay with the following modifications.

Test solution. Weigh and powder 20 tablets. Disperse a quantity of the powder containing 500 mg of Metformin Hydrochloride in solution A with the aid of ultrasound with intermittent shaking and dilute to 100.0 ml with solution A and filter.

Inject reference solution (c) and the test solution. In the chromatogram obtained with the test solution, the area of any secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.1 per cent) and the sum of the areas of all the secondary peaks is not more than 6 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.6 per cent). Ignore any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Assay

Insert before chromatographic system
Reference solution (c). A 0.0005 per cent w/v solution of *metformin hydrochloride IPRS* in solution A.

Insert at the end
Storage. Store protected from light and moisture, at a temperature not exceeding 30°.

Methadone Tablets. Page 2882

Uniformity of content
Test solution. Change **to**:
Test solution. Disperse 1 intact tablet in the mobile phase, with the aid of ultrasound with intermittent shaking and dilute with the mobile phase to obtain a solution containing 0.05 per cent w/v of Methadone Hydrochloride.

Reference solution. Change **to**:
Reference solution. A 0.05 per cent w/v solution of *methadone hydrochloride IPRS* in the mobile phase.

Methotrexate. Page 2884

Identification
Insert before A.
Test A may be omitted if tests B and C are carried out. Test B may be omitted if tests A and C are carried out.

Insert at the end
C. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with reference solution (a).

Related substances. After chromatographic system, impurity table
Change **to**:

Name	Relative retention time	Correction factor
Methotrexate impurity B[1]	0.3	---
Methotrexate impurity C[2]	0.4	---
Methotrexate impurity D[3]	0.9	---
Methotrexate (Retention time: about 18 minutes)	1.0	---
Methotrexate impurity E[4]	1.4	0.8
Methotrexate impurity I[5]	1.5	1.4
Methotrexate impurity H[6]	1.6	---

[1] (2S)-2-[[4-[[(2,4-diaminopteridin-6-yl)methyl]amino]benzoyl]amino]pentanedioic acid (4-aminofolic acid,aminopterin),
[2](2*S*)-2-[[4-[[(2-amino-4-oxo-1,4-dihydropteridin-6-yl)methyl]methylamino]benzoyl]amino]pentanedioic acid (*N*-methylfolic acid, methopterin),
[3]4-[[(2-amino-4-oxo-1,4-dihydropteridin-6-yl)methyl]methylamino]benzoic acid (N^{10}-methylpteroic acid),
[4]4-[[(2,4-diaminopteridin-6-yl)methyl]methylamino]benzoic acid (4-amino-N^{10}-methylpteroic acid, APA),
[5](4S)-4-[[4-[[(2,4-diaminopteridin-6-yl)methyl]methylamino]benzoyl]amino]-5-methoxy-5-oxopentanoic acid (methotrexate 1-methyl ester),
[6](2S)-2-[[4-[[(2,4-diaminopteridin-6-yl)methyl]methylamino]benzoyl]amino]-5-methoxy-5-oxopentanoic acid (methotrexate 5-methyl ester).

Methotrexate Injection. Page 2886

Identification
Change **from**: When examined in the range of 200 nm to 400 nm (2.4.7), a 0.001 per cent w/v solution in *0.1 M sodium hydroxide* shows absorption maxima at 258, 303 and 371 nm.
to: A. When examined in the range of 200 nm to 400 nm (2.4.7), a 0.001 per cent w/v solution in *0.1 M sodium hydroxide* shows absorption maxima at 258, 303 and 371 nm.

B. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with reference solution (a).

Methotrexate Tablets. Page 2887

Identification

Change **from**: Extract a quantity of the powdered tablets containing 10mg of Methotrexate with sufficient *0.1 M sodium hydroxide* to produce 100 ml, filter and dilute 10 ml of the filtrate to 100 ml with *0.1 M sodium hydroxide.*

When examined in the range 230 nm to 380 nm (2.4.7), the resulting solution shows absorption maxima at about 258 nm, 303 nm and 371 nm.
to: A. Extract a quantity of the powdered tablets containing 10mg of Methotrexate with sufficient *0.1 M sodium hydroxide* to produce 100 ml, filter and dilute 10 ml of the filtrate to 100 ml with *0.1 M sodium hydroxide.*

When examined in the range 230 nm to 380 nm (2.4.7), the resulting solution shows absorption maxima at about 258 nm, 303 nm and 371 nm.

B. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with reference solution (b).

Methylprednisolone Tablets. Page 2902

Dissolution. Line 1
Change **from**: Apparatus No. 1 (Basket)
to: Apparatus No. 2 (Paddle)
Line 3
Change **from**: 100 rpm and 45 minutes.
to: 50 rpm and 30 minutes.

Metoclopramide Tablets. Page 2909

Uniformity of content. *Test solution.*
Change **to:** *Test solution*. Disperse one tablet in 30 ml of *water*, with the aid of ultrasound for 20 minutes and dilute to 100.0 ml with *water*, filter.

Mitiglinide Calcium Dihydrate. Page 2950

Water
Change **from:** Not more than 7.0 per cent, determined on 0.2 g.
to: 4.5per cent to 6.0 per cent, determined on 0.2 g.

Mometasone Furoate. Page 2955

Identification
Change **to:** A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *mometasone furoate IPRS* or with the reference spectrum of mometasone furoate.

B. In the Assay, the principal peak in the chromatogram obtained with test solution (b) corresponds to the peak in the chromatogram obtained with reference solution (a).

Related substances. Change **to:**
Related substances. Determine by liquid chromatography (2.4.14).

NOTE- Prepare the solution immediately before use and protect from light.

*Solvent mixture.*50 volumes of *acetonitrile*, 50 volumes of *water* and 0.1 volume of *glacial acetic acid*.

Test solution (a). Dissolve 25.0 mg of the substance under examination in 15 ml of *acetonitrile* and dilute to 50.0 ml with the solvent mixture.

Test solution (b). Dilute 5.0 ml of test solution (a) to 25.0 ml with the solvent mixture.

Reference solution (a). Dissolve 25.0 mg of *mometasone furoate IPRS* in 15 ml of *acetonitrile* and dilute to 50.0 ml with the solvent mixture. Dilute 5.0 ml of the solution to 25.0 ml with the solvent mixture

Reference solution (b). Dilute 5.0 ml of reference solution (a) to 100.0 ml with the solvent mixture. Further dilute 1.0 m1 of the solution to 10.0 ml with the solvent mixture.

Reference solution (c). A 0.5 per cent w/v solution of *mometasone furoate for system suitability IPRS* (containing impurity C and J)in *acetonitrile.* Dilute 1.0 ml of the solution to 10.0 ml with the solvent mixture.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with end-capped octadecylsilane bonded to porous silica (5µm) (Such as Symmetry C18),
- mobile phase: a mixture of equal volumes of *acetonitrile* and *water,*
- flow rate: 1ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 20 µl.

Name	Relative retention time
Mometasone furoate impurity C[1]	0.9
Mometasone furoate (Retention time about 24 minutes)	1.0
Mometasone furoate impurity J[2]	1.5

[1]21-chloro-16α-methyl-3,11,20-trioxopregna-1,4-dien-17-yl furan-2-carboxylate,
[2]9,21-dichloro-11β-hydroxy-6α,16α-dimethyl-3,20-dioxopregna-1,4-dien-17-yl furan-2-carboxylate.

Inject reference solution (c) to identify the peaks due to mometasone furoate impurity C and J.

Inject reference solution (c). The test is not valid unless the resolution between the peaks due to mometasone furoate impurity C and mometasone furoate is not less than 2.5.

Inject reference solution (b) and test solution (a). Run the chromatogram 3.5 times the retention time of the principal peak, the area of any peak corresponding to mometasone impurity J is not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent), the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent) and the sum of the areas of all the secondary peak is not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent). Ignore any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Assay. Change **to:**
Assay. Determine by liquid chromatography (2.4.14), as described under Related substances.

Inject reference solution (a) and test solution (b).

Calculate the content of $C_{27}H_{30}Cl_2O_6$.

Mometasone Aqueous Nasal Spray. Page 2956

Identification. Change **to:**
Identification

In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with reference solution (b).

Related substances. Change **to:**
Related substances. Determine by liquid chromatography (2.4.14).

NOTE—Prepare solutions immediately before use and protect from light.

Solvent mixture A. 50 volumes of *acetonitrile*, 50 volumes of *water* and 0.1 volume of *glacial acetic acid.*

Solvent mixture B. 6 volumes of *acetonitrile* and 94 volumes of solvent mixture A.

Test solution. Discharge the container a sufficient number of times to obtain1 mg of Mometasone Furoate, add 3 ml of *acetonitrile* and 2 ml of solvent mixture A. Mix with the aid of ultrasound and dilute to 10.0 ml with solvent mixture A and centrifuge.

Reference solution (a). A 0.1 per cent w/v solution of *mometasone furoate IPRS* in *acetonitrile.*

Reference solution (b). Dilute 1.0 ml of reference solution (a) to 10.0 ml with solvent mixture B.

Reference solution (c). Dilute 1.0 ml of reference solution (b) to 200.0 ml with solvent mixture A.

Reference solution (d). A 0.5 per cent w/v of *mometasone furoate for system suitability IPRS* in *acetonitrile.* Dilute 1.0 ml of the solution to 10.0 ml with solvent mixture A.

Reference solution (e). Dilute 1.0 ml of reference solution (c) to 5.0 ml with solvent mixture A.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with end-capped octadecylsilane bonded to porous silica (5 µm) (Such as Symmetry C18),
- mobile phase: a mixture of equal volumes of *acetonitrile* and *water,*
- flow rate: 1ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 20 µl.

Name	Relative retention time
Mometasone furoate impurity C[1]	0.9
Mometasone furoate (Retention time about 24 minutes)	1.0
Mometasone furoate impurity J[2]	1.5

[1]21-chloro-16α-methyl-3,11,20-trioxopregna-1,4-dien-17-yl furan-2-carboxylate,
[2]9,21-dichloro-11β-hydroxy-6α,16α-dimethyl-3,20-dioxopregna-1,4-dien-17-yl furan-2-carboxylate.

Inject reference solution (d). The test is not valid unless the resolution between the peaks due tomometasone furoate impurity C and mometasone furoate is not less than 2.5.

Inject reference solution (c), (e) and the test solution. run the chromatogram 2.5 times the retention time of the principal peak, the area of any secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.5 per cent) and the sum of the areas of all the secondary peak is not more than 4.0 times the area of the principal peak in the chromatogram obtained with reference solution (c) (2.0 per cent). Ignore any peak with an area less than the area of the principal peak in the chromatogram obtained with reference solution (e) (0.1 per cent).

Assay. Change **to:**
Assay. Determine by liquid chromatography (2.4.14), as described under Related substances.

Inject reference solution (b) and the test solution.

Calculate the content of $C_{27}H_{30}Cl_2O_6$ in the nasal spray.

Mometasone Cream. Page 2957

Identification

Change **to: Identification**

In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with reference solution (b).

Related substances. Change **to:**
Related substances. Determine by liquid chromatography (2.4.14).

NOTE—Prepare solutions immediately before use and protect from light.

*Solvent mixture A.*50 volumes of *acetonitrile*, 50 volumes of *water* and 0.1 volume of *glacial acetic acid*.

*Solvent mixture B.*45 volumes of *acetonitrile* and 55 volumes of solvent mixture (a).

Test solution. Disperse a quantity of the cream containing about 10 mg of Mometasone Furoate in 45 ml of *acetonitrile* by heating on a water-bath at 60° with intermittent shaking for 60 minutes. Place in freezer for 30 minutes, shake with to 55 ml of solvent mixture A. Centrifuge and filter.

Reference solution (a). A0.1 per cent w/v solution of *mometasone furoate IPRS* in *acetonitrile.*

Reference solution (b). Dilute 1.0 ml of reference solution (a) to 10.0 ml with solvent mixture B.

Reference solution (c). Dilute 1.0 ml of reference solution (b) to 200.0 ml with solvent mixture B.

Reference solution (d). A 0.5 per cent w/v solution of *mometasone furoate for system suitability IPRS* (containing impurity C)in *acetonitrile.* Dilute 1.0 ml of the solution to 10.0 ml with solvent mixture A.

Reference solution (e). Dilute 2.0 ml of reference solution (c) to 10.0 ml with solvent mixture B.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with end-capped octadecylsilane bonded to porous silica (5 µm) (Such as Symmetry C18),
- mobile phase: a mixture of equal volumes of *acetonitrile* and *water,*
- flow rate: 1ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 20 µl.

Name	Relative retention time
Mometasone furoate impurity C[1]	0.9
Mometasone furoate (Retention time about 25 minutes)	1.0
Mometasone furoate impurity J[2]	1.5

[1]21-chloro-16α-methyl-3,11,20-trioxopregna-1,4-dien-17-yl furan-2-carboxylate,
[2]9,21-dichloro-11β-hydroxy-6α,16α-dimethyl-3,20-dioxopregna-1,4-dien-17-yl furan-2-carboxylate.

Inject reference solution (d). The test is not valid unless the resolution between the peaks due to mometasone furoate impurity C and mometasone furoate is not less than 2.5.

Inject reference solution (c), (e) and the test solution. Run the chromatogram 2.5 times the retention time of the principal peak, the area of any secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.5 per cent) and the sum of the areas of all the secondary peak is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (c) (1.0 per cent). Ignore any peak with an area less than the area of the principal peak in the chromatogram obtained with reference solution (e) (0.1 per cent).

Assay. Change **to:**
Assay. Determine by liquid chromatography (2.4.14), as described under Related substances.

Inject reference solution (b) and the test solution.

Calculate the content of $C_{27}H_{30}Cl_2O_6$ in the cream.

Mometasone Ointment. Page 2958

Identification

Change **to: Identification**

In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with reference solution (b).

Insert before **Other tests**

Related substances. Determine by liquid chromatography (2.4.14).

NOTE—Prepare solutions immediately before use and protect from light.

*Solvent mixture A.*50 volumes of *acetonitrile*, 50 volumes of *water* and 0.1 volume of *glacial acetic acid*.

*Solvent mixture B.*45 volumes of *acetonitrile* and 55 volumes of solvent mixture A.

Test solution. Disperse a quantity of the ointment containing about 10 mg of Mometasone Furoate in 25 ml of *acetonitrile* by heating on a water-bath at 80° and allow to cool. Add 20 ml of *acetonitrile* and 30 ml of solvent mixture A, shake for 30 minutes and dilute to 100.0 ml with solvent mixture A, centrifuge and filter.

Reference solution (a). A0.1 per cent w/v solution of *mometasone furoate IPRS* in *acetonitrile.*

*Reference solution (b).*Dilute 1.0 ml of reference solution (a)to 10.0 ml with solvent mixture B.

*Reference solution (c).*Dilute 1.0 ml of reference solution (b)to 200.0 ml with solvent mixture B.

*Reference solution (d).*A 0.5 per cent w/v solution of *mometasone furoate for system suitability IPRS* in *acetonitrile.* Dilute 1.0 ml of the solution to 10.0 ml with solvent mixture A.

Reference solution (e). Dilute 2.0 ml of reference solution (c) to 10.0 ml with solvent mixture B.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with end-capped octadecylsilane bonded to porous silica (5 µm) (Such as Symmetry C18),
- mobile phase: a mixture of equal volumes of *acetonitrile* and *water,*
- flow rate: 1ml per minute,
- spectrophotometer set at 254nm,
- injection volume: 20 µl.

Name	Relative retention time
Mometasone furoate impurity C[1]	0.9
Mometasone furoate (Retention time about 25 minutes)	1.0
Mometasone furoate impurity J[2]	1.5

[1]21-chloro-16α-methyl-3,11,20-trioxopregna-1,4-dien-17-yl furan-2-carboxylate,
[2]9,21-dichloro-11β-hydroxy-6α,16α-dimethyl-3,20-dioxopregna-1,4-dien-17-yl furan-2-carboxylate.

Injection reference solution (d) to identify the peak due to mometasone furoate impurity C and J.

Inject reference solution (d). The test is not valid unless the resolution between the peaks due to mometasone furoate impurity C and mometasone furoate is not less than 2.5.

Inject reference solution (c), (e) and the test solution. Run the chromatogram 2.5 times the retention time of the principal peak, the area of any secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.5 per cent) and the sum of the areas of all the secondary peaks is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (c) (1.0 per cent). Ignore any peak with an area less than the area of the principal peak in the chromatogram obtained with reference solution (e) (0.1 per cent).

Assay. Change **to:**
Assay. Determine by liquid chromatography (2.4.14), as described under Related substances

Inject reference solution (b) and the test solution.

Calculate the content of $C_{27}H_{30}Cl_2O_6$ in the ointment.

Montelukast Sodium. Page 2959

Related substances

Change **from**: *Reference solution (b)*. Dilute 10.0 ml of reference solution (a) to 100.0 ml with the solvent mixture. Dilute 3.0 ml of this solution to 100.0 ml with the solvent mixture.

to: *Reference solution (b)*. Transfer 3 mg of *montelukast sulphoxide isomer IPRS* to a 100-ml volumetric flask, add 3.0 ml of reference solution (a), dissolve in 30 ml of the solvent mixture and dilute to volume with the solvent mixture. Dilute 1.0 ml of the solution to 10.0 ml with the solvent mixture.

Last para, line 4

Change **from**: principal
to: corresponding

Montelukast Tablets. Page 2962

Related substances. *Reference solution (a)*
Change **to**: A solution of *montelukast sodium IPRS* containing 0.0025 per cent w/v of *montelukast* in the solvent mixture.

Reference solution (b)
Change **to**: *Reference solution (b)*. A 0.0025 per cent w/v solution of *montelukast sulphoxide isomer IPRS* in reference solution (a). Dilute 1.0 ml of the solution to 10.0 ml with the solvent mixture.

Last para, line 4
Change **from**: principal
to: corresponding

Morphine Injection. Page 2967

Identification. A
Change **to**: A. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with the reference solution.

Bacterial endotoxins. Line 2 and 4
Change **from**: morphine
to: morphine sulphate

Multiple Electrolytes and Dextrose Injection Type I. Page 2972

Assay. *For magnesium*
Change **to**: Dilute suitably with *water* and determine by Method A for atomic absorption spectrophotometry (2.4.2), measure at 285.2 nm and using magnesium solution AAS, suitably diluted with *water* for the standard solution.

Multiple Electrolytes and Dextrose Injection Type II. Page 2974

Assay. *For magnesium*
Change **to**: Dilute suitably with *water* and determine by Method A for atomic absorption spectrophotometry (2.4.2), measure at 285.2 nm and using magnesium solution AAS, suitably diluted with *water* for the standard solution.

Multiple Electrolytes and Dextrose Injection Type V. Page 2977

Assay. *For magnesium*
Change **to**: Dilute suitably with *water* and determine by Method A for atomic absorption spectrophotometry (2.4.2), measure at 285.2 nm and using magnesium solution AAS, suitably diluted with *water* for the standard solution.

Multiple Electrolytes Injection Type VI. Page 2979

Assay. *For magnesium*
Change **to**: Dilute suitably with *water* and determine by Method A for atomic absorption spectrophotometry (2.4.2), measure at 285.2 nm and using magnesium solution AAS, suitably diluted with *water* for the standard solution.

Naltrexone Hydrochloride. Page 3023

Related substances. After chromatographic system, para 1

Change **to**:

Name	Relative retention time	Correction factor
Naltrexone impurity A[1]	0.4	---
Naltrexone impurity B[2]	0.7	---
Naltrexone impurity F[3]	0.8	---

Naltrexone impurity G[4]	0.9	---
Naltrexone	1.0	---
Naltrexone impurity C[5]	1.05	---
Naltrexone impurity H[6]	1.1	---
Naltrexone impurity I[7]	1.2	---
Naltrexone impurity J[8]	1.3	---
Naltrexone impurity D[9]	1.4	0.4
Naltrexone impurity E[10]	1.7	---

[1]17-formyl-4,5α-epoxy-3,14- dihydroxymorphinan-6-one,
[2]4,5α-epoxy-3,14-dihydroxymorphinan-6-one (noroxymorphone),
[3]17-(cyclopropylmethyl)-4,5α-epoxy-3,10α,14-trihydroxymorphinan-6-one,
[4]17-(cyclopropylmethyl)-4,5α-epoxy-3,10β,14-trihydroxymorphinan-6-one,
[5]17- but-3-enyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-one,
[6]17-butyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-one,
[7]17-(cyclopropylmethyl)-4,5α-epoxy-3,14- dihydroxymorphinan-6,10-dione,
[8]7-(cyclopropylmethyl)-4,5α-epoxy-14-hydroxy- 3-methoxymorphinan-6-one,
[9]17,17′-bis(cyclopropylmethyl)-4,5α:4′,5′-α-diepoxy- 3,3′,14,14′-tetrahydroxy-2,2′-bimorphinanyl-6,6′-dione(pseudonaltrexone),
[10]3- (cyclopropylmethoxy)-17-(cyclopropylmethyl)-4,5α-epoxy-14- hydroxymorphinan-6-one.

Inject reference solution (b). The test is not valid unless the resolution between the peaks due to naltrexone and naltrexone impurity C is not less than 2.0.

Norfloxacin. Page 3083

Related substances. *Reference solution (a)*
Change **to:** *Reference solution (a).*A 0.004 per cent w/v solution of *norfloxacin IPRS* in solution A. Dilute 1.0 ml of the solution to 100.0 ml with solution A.

Insert before chromatographic system
Reference solution (c). Dissolve 4 mg of *norfloxacin for peak identification IPRS* (containing impurity K) in 10.0 ml of solution A.

After chromatographic system, para 1
Change **from:** The relative retention time with reference to norfloxacin for norfloxacin impurity E (7-chloro-l-ethy1-4-oxo-6-(piperazin-1-y1)-1,4-dihydroquinoline-3-carboxylic acid)is about 0.97, for norfloxacin impurity A (7-chloro- 1 -ethy1-6-fluoro-4-oxo- 1,4-dihydroquinoline-3-carboxylic acid) is about 1.5 and for norfloxacin impurity H (7-[4-(ethoxycarbonyl)piperazin-l-y1]-1- ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid) is about 1.6.

to:

Name	Relative retention time
Norfloxacin impurity K[1]	0.6
Norfloxacin impurity E[2]	0.97
Norfloxacin (Retention time: about 11 minutes)	1.0
Norfloxacin impurity A[3]	1.5
Norfloxacin impurity H[4]	1.6

[1]6-fluoro-1-methyl-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid.
[2]7-chloro-1-ethyl-4-oxo-6-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid,
[3]7-chloro-l-ethyl-6-fluoro-4-oxo-l,4-dihydroquinoline-3-carboxylic acid,
[4]7-[4- (ethoxycarbonyl) piperazin-1-yl)-l-ethyi-6-fluoro-4-oxo-l,4-dihydroquinoline-3-carboxylic acid,

Inject reference solution (b) to identify the peaks due to norfloxacin impurity A, E and H and reference solution (c) to identify the peak due to norfloxacin impurity K.

Last para, lines 3 to 5
Change **to**: …any peak corresponding to norfloxacin impurity E and norfloxacin impurity K, each of, is not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent), the area of any other secondary…

Norfloxacin Tablets. Page 3084

Insert before **Other tests**
Related substances. Determine by liquid chromatography (2.4.14).

Solvent mixture. 95 volumes of *water,* adjusted to pH 2.0 with *orthophosphoric acid* and 5 volumes of *acetonitrile.*

Test solution. Disperse a quantity of powdered tablets containing 0.2 g of Norfloxacin in the solvent mixture, with the aid of ultrasound and dilute to 500.0 ml with the solvent mixture, filter.

Reference solution (a). A 0.004 per cent w/v solution of *norfloxacin IPRS* in the solvent mixture. Dilute 1.0 ml of the solution to 100.0 ml with the solvent mixture.

Reference solution (b). A 0.04 per cent w/v solution of *norfloxacin for system suitability IPRS* in the solvent mixture.

Reference solution (c). A 0.04 per cent w/v solution of *norfloxacin for peak identification IPRS* in the solvent mixture.

Chromatographic system

-a stainless steel column 25 cm x 4.6 mm, packed with end-capped amidohexadecylsilyl bonded to porous silica (5 µm) (Such as Supelcosil LC-ABZ),
- column temperature: 60°,
- mobile phase: A. *water,* adjusted to pH 2.0 with *orthophosphoric acid,*
  B. *acetonitrile,*
- a gradient programme using the conditions given below,
-flow rate: 1 ml per minute,
- spectrophotometer set at 265 nm,
- injection volume: 20 µl.

Time (in min)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	95	5
5	95	5
7	93	7
10	87	13
15	47	53
20	10	90
22	10	90
23	95	5
26	95	5

Name	Relative retention time
Norfloxacin impurity K[1]	0.6
Norfloxacin impurity E[2]	0.97
Norfloxacin (Retention time: about 11 minutes)	1.0
Norfloxacin impurity A[3]	1.5
Norfloxacin impurity H[4]	1.6

[1]6-fluoro-1-methyl-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid,
[2]7-chloro-1-ethyl-4-oxo-6-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid,
[3]7-chloro-l-ethyl-6-fluoro-4-oxo-l,4-dihydroquinoline-3-carboxylic acid,
[4]7-[4- (ethoxycarbonyl) piperazin-1-yl)-l-ethyl-6-fluoro-4-oxo-l,4-dihydroquinoline-3-carboxylic acid.

Inject reference solution (b) to identify the peaks due to norfloxacin impurity A, E and H and reference solution (c) to identify the peak due to norfloxacin impurity K.

Inject reference solution (b). The test is not valid unless the resolution between the peaks due to norfloxacin impurity A and norfloxacin impurity H is not less than 3.0 and the peak-to-valley ratio is not less than 5.0, where H_p is the height above the baseline of the peak due to norfloxacin impurity E and H_v is the height above the baseline of the lowest point of the curve separating this peak from the peak due to norfloxacin.

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to norfloxacin impurity E and norfloxacin impurity K, each of, is not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent), the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent) and the sum of the areas of all the secondary peaks is not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent). Ignore any peak with an area less than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent).

Loss on ignition. Line 1
Change **from**: **Loss on ignition** (2.4.20).
to: **Sulphated ash** (2.3.18).

Olmesartan Medoxomil and Hydrochlorothiazide Tablets. Page 5245

Related substances. Change **to**:

Related substances. Determine by liquid chromatography (2.4.14).

NOTE - Prepare the solutions immediately before use.

Solvent mixture. Equal volumes of *acetonitrile* and *water*.

Test solution. Disperse a quantity of powdered tablets containing 50 mg of Olmesartan Medoxomil in the solvent mixture, with the aid of ultrasound with intermittent shaking and dilute to 50.0 ml with the solvent mixture. Centrifuge a portion of the solution, filter.

Reference solution. A 0.001 per cent w/v solution of *olmesartan medoxomil IPRS* in the solvent mixture.

Chromatographic system
– a stainless steel column 10 cm x 4.6 mm, packed with octylsilane bonded to porous silica (3.5 µm) (Such as Symmetry C8),
– column temperature: 40°,
– mobile phase: A. a buffer solution prepared by dissolving 4.08 g of *potassium dihydrogen orthophosphate* in 850 ml of *water*, adjusted to pH 2.5 with *orthophosphoric acid* and dilute to 1000 ml with *water*.
B. *acetonitrile,*
– a gradient programme using the conditions given below,
– flow rate: 1 ml per minute,
– spectrophotometer set at 250 nm,
– injection volume: 10 µl.

Time (in min)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	85	15
6	85	15
8	83	17
20	83	17
30	40	60
35	85	15
40	85	15

The relative retention time with reference to olmesartan medoxomil for olmesartan impurity (1-{[2′-(1*H*-Tetrazol-5-yl)biphenyl-4-yl]methyl}-4-(2-hydroxypropan-2-yl)- 2-propyl-1*H*-imidazole-5-carboxylic acid) is about 0.65.

Inject the reference solution. The test is not valid unless the tailing factor is not more than 2.0 and the relative standard deviation of replicate injections is not more than 5.0 per cent.

Inject the reference solution and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to olmesartan is not more than 2.5 times the area of the principal peak in the chromatogram obtained with the reference solution (2.5 per cent), the area of any other secondary peak is not more than 0.5 times the area of the principal peak in the chromatogram obtained with the reference solution (0.5 per cent) and the sum of the areas of all the secondary peaks is not more than 4.1 times the area of the principal peak in the chromatogram obtained with the reference solution (4.1 per cent). Ignore any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with the reference solution (0.1 per cent).

Olopatadine Ophthalmic Solution. Page 3114

Line 1, Insert the following

"Olopatadine Eye Drops, Olopatadine Hydrochloride Eye Drops"

Related substances. A. After chromatographic system, para 2
Change **to**: Inject reference solution (b) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to olopatadine E isomer is not more than 0.005 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent), the area of any peak corresponding to olopatadine impurity B is not more than 0.02 times the area of the principal peak in the chromatogram obtained with reference solution (b) (2.0 per cent), the area of any peak corresponding to olopatadine carbaldehyde is not more than 0.005 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent) and area of any other secondary peak is not more than 0.005 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent). Ignore any peak at relative retention time of more than 1.5.

Omeprazole. Page 3116

Related substances. Change **to:**
Related substances. Determine by liquid chromatography (2.4.14).
NOTE- Prepare the solutions immediately before use.

*Solvent mixture.*75 volumes of mobile phase A and 25 volumes of *acetonitrile*.

Test solution. Dissolve 60 mg of the substance under examination in the solvent mixture and dilute to 100.0 ml with the solvent mixture.

Reference solution (a). A solution containing 0.06 per cent w/v of *omeprazole IPRS* and 0.00006 per cent w/v, each of, *omeprazole related compound A IPRS, omeprazole related compound E IPRS, omeprazole related compound I IPRS* and5-methoxy-1*H*-benzimidazol-2-thiolin the solvent mixture.

Reference solution (b). A 0.0006 per cent w/v solution of *omeprazole IPRS* in the solvent mixture.

Reference solution (c). Dilute 1.0 ml of reference solution (b) to 20.0 ml with the solvent mixture.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with octylsilane bonded to porous silica (5 µm),
- sample temperature: 4°,
- mobile phase: A. a buffer solution prepared by dissolving 0.181 g of *sodium dihydrogen orthophosphate* and 1.12 g of *disodium hydrogen orthophosphateanhydrous* in 1000 ml of *water,* adjusted to pH 7.0 with *orthophosphoric acid,*
B. *acetonitrile*,
- a gradient programme using the conditions given below,
- flow rate: 0.8ml per minute,
- spectrophotometer set at 264 nm,
- injection volume: 40 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	75	25
12	75	25
22	50	50
45	50	50
45.1	75	25
50	75	25

Name	Relative retention time	Correction factor
5-Methoxy-1H-benzimidazol-2-thiol	0.41	---
Omeprazole N-oxide (omeprazole related compound E)[1]	0.53	0.75
Omeprazole sulfone N-oxide (omeprazole related compound I)[2]	0.58	0.68
Desmethoxy omeprazole[3]	0.97	---
Omeprazole	1.0	---
Omeprazole sulfone (omeprazole related compound A)[4]	1.07	---
Omeprazole 4-chloro analog[5]	1.16	---
Ufiprazole[6]	1.25	---

Omeprazole thioxo pyrido analogs[7]	1.55 and 1.64	---

[1]4-Methoxy-2-[[(*RS*)-(5-methoxy-1*H*-benzimidazol-2-yl)sulfinyl]methyl]-3,5-dimethylpyridine 1-oxide.
[2]4-Methoxy-2-[[(5-methoxy-1*H*-benzimidazol-2-yl)sulfonyl]methyl]-3,5-dimethylpyridine 1-oxide.
[3] 2-[(*RS*)-[(3,5-Dimethylpyridin-2-yl)methyl]sulfinyl]-5-methoxy-1*H*-benzimidazole.
[4]5-Methoxy-2-[[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulfonyl]-1*H*-benzimidazole.
[5] 2-[(*RS*)-[4-Chloro-3,5-dimethylpyridin-2-yl)methyl]sulfinyl]-5-methoxy-1*H*-benzimidazole.
[6] 5-Methoxy-2-((4-methoxy-3,5-dimethylpyridin-2-yl)methylthio)-1*H*-benzimidazole.
[7] Omeprazole related compounds F and G (1,3-dimethyl-8-methoxy-12-thioxopyrido[1′,2′:3,4]imidazo[1,2-a]benzimidazol-2(12*H*)-one and 1,3-dimethyl-9-methoxy-12-thioxopyrido[1′,2′:3,4]imidazo[1,2-a]benzimidazol-2(12*H*)-one). These impurities are controlled in the test for *Limit of Omeprazole Related Compounds F and G*.

Inject reference solution (a), (b) and (c). The test is not valid unless the resolution between the peaks due to omeprazole and omeprazole related compound A is not less than 2.0 in the chromatogram obtained with reference solution (a), the relative standard deviation for replicate injections is not more than 5.0 per cent in the chromatogram obtained with reference solution (b) and the signal-to-noise ratio of the principal peak is not less than 10 in the chromatogram obtained with reference solution (c).

Inject reference solution (b) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to 5-methoxy-1H-benzimidazol-2-thiol, omeprazole N-oxide, omeprazole sulfone N-oxide, desmethoxy omeprazole, omeprazole sulfone, omeprazole 4-chloro analog and ufiprazole, each of, is not more than 0.15 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent), the area of any other secondary peak is not more 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent) and the sum of the areas of all the secondary peaks is not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent). Ignore any peak with an area less than 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).
Limit of Omeprazole related compound F and G. Measure the absorbance of 2.0 per cent w/v solution of Omeprazole in *methylene chloride* at about 440 nm (2.4.7) using 1 cm cell. The absorbance is not more than 0.10 corresponding to not more than 350 ppm of the sum of omeprazole related compound F and G.

Omeprazole Gastro-resistant Capsules. Page 3118

Insert before **Other tests**
Related substances. Determine by liquid chromatography (2.4.14).

Solvent mixture. Dissolve 3.8 g of *sodium borate decahydrate* in about 400 ml of *water*. Add 0.5 g of *edetate disodium* and adjusted to pH 11.0 with 50 per cent w/v solution of *sodium hydroxide*. Transfer the solution to a 1000-ml volumetric flask, add 200 ml of *ethanol* and dilute to volume with *water.*

Test solution. Disperse a quantity of mixed contents of capsules containing 20 mg of Omeprazole in 50 ml of the solvent mixture, with the aid of ultrasound for 15 minutes and dilute to 100.0 ml with the solvent mixture.

Reference solution (a). A 0.0001 per cent w/v solution of *omeprazole IPRS* in the solvent mixture.

Reference solution (b). A solution containing 0.02 per cent w/v of *omeprazole IPRS* and 0.0001 per cent w/v, each of, *omeprazole related compound F and G mixture IPRS* and5-methoxy-1H-benzimidazol-2-thiolin the solvent mixture, sonicate for 15 minutes and then heat at 55° for 30 minutes.

NOTE—The heating step facilitates conversion of omeprazole related compounds F and G into a product with the relative retention time of 0.33. The remaining unconverted omeprazole related compounds F and G may elute as a very broad peak at the relative retention time of about 0.5.

Chromatographic system
– a stainless steel column 15 cm × 4.6 mm, packed with base-deactivated octylsilane bonded to porous silica (5 µm) (Such as Luna C8),
– mobile phase: A. a buffer solution prepared by dissolving 3 g of *glycine* in 750 ml of *water,* adjusted to pH9.0 with a 50.0 per cent w/v solution of *sodium hydroxide* and dilute to 1000 ml with *water,*
B. a mixture of 85 volumes of *acetonitrile* and 15 volumes of *methanol*,
– a gradient programme using the conditions given below,
– flow rate: 1.2 ml per minute,
– spectrophotometer set at 305nm,
– injection volume: 10 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	88	12
20	40	60
21	88	12
25	88	12

Name	Relative retention time	Correction factor
Omeprazole related compounds F and G[1*]	0.33	0.63
5-methoxy-1H-benzimidazol-2-thiol	0.64	0.32
Omeprazole	1.0	-

*These impurities undergo transformation in the solution to form a conversion product, which elutes at the relative retention time of 0.33, [1]1,3-Dimethyl-8-methoxy-12-thioxopyrido[1′,2′:3,4]imidazo[1,2-*a*]benzimidazol-2(12*H*)-oneand1,3-dimethyl-9-methoxy-12-thioxopyrido [1′,2′:3,4]imidazo[1,2-*a*]benzimidazol-2(12*H*)-one.

Inject reference solution (b) to identify the peaks due to omeprazole related compounds F and G and 5-methoxy-1H-benzimidazol-2-thiol.

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to omeprazole related compounds (F and G) and 5-methoxy-1H-benzimidazol-2-thiol, each of, is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent), the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent) and the sum of the areas of all the secondary peaks is not more than 4.0 times the area of the principal peak in the chromatogram obtained with reference solution (a) (2.0 per cent).

Assay. Change **to:**

Assay. Determine by liquid chromatography (2.4.14), as described under Related substances with the following modifications.

Reference solution. A 0.02 per cent w/v solution of *omeprazole IPRS* in the solvent mixture.

Inject the reference solution. The test is not valid unless the column efficiency is not less than 20000 theoretical plates, the tailing factor is not less than 0.8 and not more than 2.0, and the relative standard deviation for replicate injections is not more than 2.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{17}H_{19}N_3O_3S$ in the capsules.

Ondansetron Tablets. Page 3126

Identification. Line 3

Change **from**: chromatogram obtained with the reference solution (a).

to: chromatogram obtained with the reference solution.

Orphenadrine Hydrochloride. Page 3134

Identification. A

Insert at the end

"or with the reference spectrum of orphenadrine hydrochloride."

Oxcarbazepine. Page 3149

Related substances. Change **to**:

Related substances

A. Determine by liquid chromatography (2.4.14).

NOTE- Related substances B should be used, If oxcarbazepine related compound A and oxcarbazepine related compound B are known process impurities.

Test solution. Dissolve 50 mg of the substance under examination in the mobile phase and dilute to 100.0 ml with the mobile phase.

*Reference solution (a).*A 0.0025 per cent w/v solution of *oxcarbazepine IPRS* in the mobile phase. Dilute 1.0 ml of the solution to 100.0 ml with the mobile phase.

*Reference solution (b).*A solution containing0.01 per cent w/v, each of, *oxcarbazepine IPRS* and *carbamazepine IPRS* in the mobile phase.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with base deactivated octadecylsilane bonded to porous silica (5µm) (Such as Hypersil BDS C-18),
- column temperature 50°,
- mobile phase: a mixture of 22 volumes of *methanol,* 16 volumes of *acetonitrile* and 62 volumes of a buffer solution prepared by dissolving 6.8 g of *potassium dihydrogen orthophosphate* in 1000 ml of *water*, add 2 ml of *triethylamine*, adjust to pH 6.0 with *orthophosphoric acid,*
- flow rate: 1.5 ml per minute,
- spectrophotometer set at 215 nm,
- injection volume: 10 µl.

Name	Relative retention Time	Correction factor
Oxcarbazepine	1.0	-
Carbamazepine[1]	1.7	0.53
Oxcarbazepine related compound E[2]	2.1	0.83
Methoxycarbamazepine[3]	2.5	0.63
Carbamazepine related compound B[4]	7.4	0.77
Methoxydibezapine[5]	7.9	0.67

[1] 5H-Dibenz[b,f]azepine-5-carboxamide.
[2]10(11H)-oxo-5H-Dibenz[b,f]azepine
[3] 10-Methoxy-5H-Dibenz[b,f]azepine-5-carboxamide.
[4] 5H-Dibenz[b,f]azepine.
[5] 10-Methoxy-5H-Dibenz[b,f]azepine.

Inject reference solution (a) and (b). The test is not valid unless the resolution between the peaks due to oxcarbazepine and carbamazepine is not less than 8.0 in the chromatogram obtained with reference solution (b) and the relative standard deviation for replicate injection is not more than 10 per cent in the chromatogram obtained with reference solution (a).

Inject reference solution (a) and the test solution. Run the chromatogram 10 times the retention time of the principal peak. The area of any peak corresponding to carbamazepine is not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent), the area of any peak corresponding to oxcarbazepine related compound E, methoxycarbamazepine, carbamazepine related compound B, and methoxydibezapine, each of, is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent), the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent) and the sum of the areas of all the secondary peaks is not more than 20 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent).

B. Determine by liquid chromatography (2.4.14)

Buffer solution. Equal volumes of 0.36 per cent w/v solution of *disodium edentate* and a solution containing 0.054 per cent w/v of *potassium dihydrogen orthophosphate* and 0.9 per cent w/v of *dibasic sodium phosphate*.

Solvent mixture. Equal volumes of *acetonitrile* and 0.18 per cent w/v solution of *ascorbic acid* in *water*.

Test solution. Dissolve 50 mg of the substance under examination in the solvent mixture and dilute to 50.0 ml with the solvent mixture.

Reference solution (a). A 0.01 per cent w/v solution of *oxcarbazepine IPRS* in *acetonitrile.* Dilute 1.0 ml of the solution to 50.0 ml with the solvent mixture.

Reference solution (b). A solution containing 0.0002 per cent w/v, each of, *oxcarbazepine related compound A IPRS*, *oxcarbazepine related compound B IPRS, oxcarbazepine related compound D IPRS*, and *oxcarbazepine related compound E IPRS* in the solvent mixture.

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (3µm) (Such as YMC-pack ODS–AQ),
- column temperature 50°,
- mobile phase A: a mixture of 75 volumes of *water,*10 volumes of the buffer solution, 10 volumes of *tetrahydrofuran*, and 5 volumes of *acetonitrile,*

B: a mixture of 60 volumes of *acetonitrile,*10 volumes of *tetrahydrofuran*, 10 volumes of the buffer solution, 20 volumes of *water,*
- a gradient programme using the conditions given below,
- flow rate: 0.8 ml per minute,
- spectrophotometer set at 240 nm,
- injection volume: 50 µl.

Time (in minutes)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	80	20
1	80	20
29	30	70
30	30	70
33	80	20
42	80	20

Name	Relative retention Time	Correction factor
Oxcarbazepine related compound F[1]	0.76	1.69
Oxcarbazepine	1.0	-
N-Carbamoyl oxcarbazepine[2]	1.1	1.10
Oxcarbazepine related compound A[3]	1.2	0.91
Oxcarbazepine related compound B[4]	1.3	0.91
Dibenzazepinodione[5]	1.7	0.50
Oxcarbazepine related compound D[6]	2.3	0.59
Oxcarbazepine related compound E[7]	2.4	0.30

[1]10,11-Dioxo-10,11-dihydro-5H-dibenzo[b,f]azepine-5-carboxamide,
[2]N-Carbamoyl-10-oxo-10,11-dihydro-5H-dibenzo[b,f]azepine-5-carboxamide,
[3]N-Formyl-10-oxo-10,11-dihydro-5H-dibenzo[b,f]azepine-5-carboxamide,
[4]N-Acetyl-10-oxo-10,11-dihydro-5H-dibenzo[b,f]azepine-5-carboxamide,
[5]5H-Dibenzo[b,f]azepine-10,11-dione,
[6]10-(10-Oxo-10,11-dihydro-5H-dibenzo[b,f]azepine-5-carboxamido)-5H-dibenzo[b,f]azepine-5-carboxamide,
[7]10(11H)-oxo-5H-Dibenz[b,f]azepine.

Inject reference solution (a) and (b) The test is not valid unless the resolution between the peaks due to oxcarbazepine related compound A and oxcarbazepine related compound B is not less than 1.0, and between oxcarbazepine related compound D and oxcarbazepine related compound E is not less than 1.2 in the chromatogram obtained with reference solution (b) and the relative standard deviation for replicate injection is not more than 5.0 per cent in the chromatogram obtained with reference solution (a).

Inject reference solution (a) and the test solution, In the chromatogram obtained with the test solution, the area of any peak corresponding to oxcarbazepine related compound F, A and D, each of, is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent), the area of any peak corresponding to *N*-carbamoyl oxcarbazepine and oxcarbazepine related compound E, each of, is not more than 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent), the area of any peak corresponding to oxcarbazepine related compound B and dibenzazepinodione,each of, is not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent), the area of any other secondary peak is not more than 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent) and the sum of the areas of all the secondary peaks is not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent). Ignore any peak with an area less than 0.15 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.03 per cent).

Oxcarbazepine Tablets. Page 3149

Related substances. Change **to:**

Related substances

A. Determine by liquid chromatography (2.4.14).

NOTE – On the basis of the synthetic route, perform either Related substances A or Related substances B. if methoxycarbamazepine is a potential degradation product, Related substances A is recommended. if carbamazepinedione or dibenzazepinodione is a potential degradation product Related substances B is recommended.

Solvent mixture. 60 volumes of *methanol* and 40 volumes of *water*.

Test solution. Disperse a quantity of the powdered tablets containing 0.5 g of Oxcarbazepine in 250 ml of the solvent mixture, with the aid of ultrasound for 15 minutes with intermittent shaking, cool to room temperature and dilute to 500.0 ml with the solvent mixture, filter. Dilute 5.0 ml of the filtrate to 10.0 ml with the mobile phase.

Reference solution (a). A 0.005 per cent w/v solution of *oxcarbazepine IPRS* in the mobile phase. Dilute 1.0 ml of the solution to 100.0 ml with the mobile phase.

Reference solution (b). A solution containing 0.05 per cent w/v of *oxcarbazepine IPRS* and 0.0001 per cent w/v of *carbamazepine IPRS* in the mobile phase.

Chromatographic system
– a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (Such as Hypersil BDS C-18),
– column temperature 50°,
– sample temperature 5°,
– mobile phase: a mixture of 29 volumes of *methanol,* 21 volumes of *acetonitrile* and 75 volumes of a buffer solution prepared by dissolving 6.8 g of *potassium dihydrogen orthophosphate* in 1000 ml *water*, add 2 ml of *triethylamine,* adjust to pH 6.0 with *orthophosphoric acid,*
– flow rate: 1.5 ml per minute,
–spectrophotometer set at 215 nm,
–injection volume: 10 µl.

Name	Relative retention time	Correction factor
Oxcarbazepine	1.0	---
Carbamazepine[1]	1.6	0.67
Dibenzazepepione[2]	2.0	---
Methoxycarbamazepine[3]	2.3	0.77

[1] 5H-Dibenz[b,f]azepine-5-carboxamide.
[2]10(11H)-Oxo-5H-dibenz[b,f]azepine.
[3]10-Methoxy-5H-dibenz[b,f]azepine-5-carboxamide.

Inject reference solution (a) and (b). The test is not valid unless the resolution between the peaks due to oxcarbazepine and carbamazepine is not less than 8.0 in the chromatogram obtained with reference solution (b) and the relative standard deviation for replicate injection is not more than 10 per cent in the chromatogram obtained with reference solution (a).

Inject reference solution (a) and the test solution. Run the chromatograms 10 times the retention time of the principal peak. In the chromatogram obtained with the test solution, the area of any peak corresponding to carbamazepine is not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.50 per cent), the area of any peak corresponding to dibenzazepepione and methoxycarbamazepine, each of, is not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent), the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent) and the sum of the areas of all the secondary peaks is not more than 7.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.75 per cent).

B. Determine by liquid chromatography (2.4.14).

Solvent mixture. 99 volumes of 0.18 per cent w/v solution of *ascorbic acid* in *water*, and 1 volume of *acetonitrile*.

Test solution. Disperse a quantity of powdered tablets containing 375 mg of oxcarbazepine in 150 ml of *acetonitrile* with the aid of ultrasound for 15 minutes with intermittent shaking, dilute to 250.0 ml with *acetonitrile,* mix and allow the suspension to settle for 30 minutes, use the supernatant. Transfer 10.0 ml of the supernatant to a 50-ml volumetric flask, add 25 ml of the solvent mixture and dilute to volume with *acetonitrile*, filter. (*NOTE- Sonicator temperature should not exceed 23°)*

Reference solution (a). A 0.0012 per cent w/v solution of *carbamazepine IPRS* in *acetonitril*e. Transfer 5.0 ml of the solution to a 100-ml volumetric flask, add 50 ml of the solvent mixture and dilute the volume with *acetonitrile*.

*Reference solution (b).*A solution containing 0.0001 per cent w/v of *oxcarbazepine related compound C IPRS* and 0.0012 per cent w/v of *carbamazepine IPRS* in *acetonitrile.* Transfer 5.0 ml of the solution to 100-ml volumetric flask, add 50 ml of the solvent mixture and dilute to volume with *acetonitrile.*

Chromatographic system

– a stainless steel column 25 cm x 3.0 mm, packed with octadecylsilane bonded to porous silica (5µm) (Such as Nucleosil C18 AB),
– column temperature 35°,
– sample temperature 5°,
– mobile phase: A. a mixture of 85 volumes of a buffer solution prepared by dissolving 4.2 g of *tris (hydroxymethyl) amino methane* and 0.2 g of *disodium edetate* in 1000 ml of *water*, 10 volumes of *tetrahydrofuran* and 5 volumes of *acetonitrile*, B. a mixture of 20 volumes of a buffer solution prepared by dissolving 18 g of *tris (hydroxylmethyl) amino methane* and 0.9 g of *disodium edetate* in 1000 ml of *water*, 10 volumes of *tetrahydrofuran* and 70 volumes of *acetonitrile,*
–a gradient programme using the conditions given below,
– flow rate: 0.5 ml per minute,
–spectrophotometer set at 254 nm,
–injection volume: 20 µl.

Time (in minutes)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	95	5
33.0	30	70
33.1	95	5
45.0	95	5

Name	Relative retention time	Correction factor
Carbamazepinedione[1]	0.72	1.43
Oxcarbazepine	1.0	–
Oxcarbazepine related compound C[2*]	1.3	–
Carbamazepine[3]	1.4	–
Dibenzazepinodione[4]	1.7	0.36

*This is a process impurity that is included in the table for identification purposes only. It is controlled in the drug substance and is not to be reported or included in the total degradation products for the drug product,
[1]10,11-Dioxo-10,11-dihydro-5H-dibenzo[b,f]azepine-5-carboxamide
[2] Acridin-9(10H)-one
[3]5H-Dibenz[b,f]azepine-5-carboxamide.
[4]5H-Dibenzo[b,f]azepine-10,11-dione.

Inject reference solution (a) and (b). The test is not valid unless the resolution between the peaks due to oxcarbazepine related compound C and carbamazepine is not less than 1.2 in the chromatogram obtained with reference solution (b) and the relative standard for replicate injections is not more than 15.0 per cent in the chromatogram obtained with reference solution (a).

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to carbamazepinedione and dibenzazepinodione, each of, is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent), the area of any peak corresponding to carbamazepine is not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent), the area of any other secondary peak is not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent) and the sum of the areas of all the secondary peaks is not more than 5.0 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent).

Oxybutynin Tablets. Page 3155

Identification

Change **to**: **Identification**

A. Disperse a quantity of the powdered tablets containing 25 mg of Oxybutynin Hydrochloride in 20 ml of *water*, adjust to pH 12 with *2 M sodium hydroxide* and extract with four 20-ml quantities of *hexane*. Filter the collected hexane layers through *anhydrous sodium sulphate* and evaporate to dryness. On the residue, determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum obtained with *oxybutynin hydrochloride IPRS*, treated in the same manner or with the reference spectrum of oxybutynin.

B. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with the reference solution.

Pantoprazole Sodium. Page 5249

Related substances. B, impurity table, line 15 and 16

Change **from**: Pantoprazole dimer (pantoprazole related compound B)
to: Pantoprazole sulphide (pantoprazole related compound B)

Pantoprazole Gastro-resistant and Domperidone Prolonged-release Capsules. Page 3190

Dissolution. *For Pantoprazole Sodium*
B. *Test solution*
Insert at the end
Dilute, if necessary, with the dissolution medium.

Related substances. *For pantoprazole*
Reference solution
Change **from**: A 0.00004 per cent w/v solution of *pantoprazole sodium IPRS* in the solvent mixture.
to: A solution of *pantoprazole sodium IPRS* containing 0.00004 per cent w/v of pantoprazole in the solvent mixture.

Parecoxib Sodium. Page 3204

Assay. Lastpara, line 1
Change **from**: 0.039241
to: 0.03924

Paroxetine Prolonged-release Tablets. Page 3208

Assay. Chromatographic system, lines 1 to 3
Change **from**: a stainless steel column 25 cm x 4.6 mm packed with octadecylsilane bonded to porous silica (5 µm) (Such as Zorbax TMS),
to: a stainless steel column 25 cm x 4.6 mm, packed with trimethylsilane bonded to porous silica (5 µm) (Such as Zorbax TMS),

Phenindione. Page3241

Line 4
Change **from**: not more than100.5 per cent
to: not more than102.0 per cent

Identification

Change **to**: A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *phenindione IPRS* or with the reference spectrum of phenindione.

B. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with reference solution (a).

Related substances. Change **to**:
Related substances. Determine by liquid chromatography (2.4.14).

NOTE — Prepare the solutions immediately before use.

Test solution. Dissolve 25 mg of the substance under examination in *methanol* and dilute to 10.0 ml with *methanol*.

Reference solution (a). A 0.00125 per cent w/v solution of *phenindione IPRS* in *methanol*.

Reference solution (b). A solution containing 0.0005 per cent w/v, each of, *phenindione IPRS*, *phenindione impurity C (*phenylacetic acid*), phenindione impurity D (*benzalphthalide) and *phenindione impurity E (*phthalic acid)in *methanol*.

Reference solution (c). Dilute 1.0 ml of reference solution (a) to 10.0 ml with *methanol*.

Chromatographic system
- a stainless steel column 10 cm x 4.6 mm, packed with end-capped octadecylsilane bonded to porous silica (3.5 µm) (Such as X-bridge shield C18),
- sample temperature: 4º,

– mobile phase: A. a mixture of 10 volumes of *acetonitrile*, 10 volumes of 1.36 per cent w/v solution of *dipotassium hydrogen orthophosphate* previously adjusted to pH 3.0 with *orthophosphoric acid* and 80 volumes of *water*,
B. a mixture of 90 volumes of *acetonitrile* and 10 volumes of *water*,
– a gradient programme using the conditions given below,
– flow rate: 1.5 ml per minute,
– spectrophotometer set at 220 nm,
– injection volume: 10 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	80	20
0.5	80	20
10	50	50
13	50	50
21	30	70
22	80	20
25	80	20

Name	Relative retention time
Phenindione impurity E[1]	0.2
Phenindione impurity C[2]	0.4
Phenindione impurity A[3]	0.6
Phenindione (Retention time: about 7 minutes)	1.0
Phenindione impurity D[4]	1.8
Phenindione impurity B[5]	2.4

[1]phthalic acid,
[2]phenylacetic acid,
[3]2-hydroxy-2-phenyl-1*H*-indene-1,3(2*H*)-dione,
[4]3-benzylidene-2-benzofuran-(3*H*)-one (benzalphthalide),
[5]2'-diphenyl-1*H*,1'*H*-[2,2'-bi-indene]-1,1',3,3'(2*H*,2'*H*)tetrone.

Inject reference solution (b). The test is not valid unless the resolution between the peaks due to phenindione impurity E and phenindione impurity C is not less than 4.6.

Inject reference solution (a), (c) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to phenindione impurity A and phenindione impurity B, each of, is not more than 0.6 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent), the area of any other secondary peak is not more than 0.4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent) and the sum of areas of all the secondary peaks is not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.5 per cent). Ignore any peak with an area less than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Assay. Change **to**:

Assay. Determine by liquid chromatography (2.4.14).

NOTE — Prepare the solutions immediately before use.

Solvent mixture. 2 per cent v/v solution of *glacial acetic acid* in *acetonitrile*.

Test solution. Dissolve 25 mg of the substance under examination in 20 ml of *0.01 M sodium hydroxide*, with the aid of ultrasound, add 50 ml of the solvent mixture and dilute to 100.0 ml with the solvent mixture.

Reference solution (a). Dissolve 25 mg of *phenindione IPRS* in 20 ml of *0.01 M sodium hydroxide*, add 50 ml of the solvent mixture and dilute to 100.0 ml with the solvent mixture.

Reference solution (b). Dissolve 5 mg, each of, *phenindione IPRS* and *phenindione impurity C*(phenylacetic acid)in 5 ml of *0.01 M sodium hydroxide*, add 5 ml of the solvent mixture and dilute to 20.0 ml with the solvent mixture.

Chromatographic system
– a stainless steel column 25 cm x 4.6 mm, packed with end-capped octadecylsilane bonded to porous silica (5 µm) (Such as Symmetry C18),
– sample temperature: 4º,
– mobile phase: a mixture of 60 volumes of 0.68 per cent w/v solution of *potassium dihydrogen orthophosphate* previously adjusted to pH 3.5 with *orthophosphoric acid* and 40 volumes of *acetonitrile*,
– flow rate: 1 ml per minute,
– spectrophotometer set at 250 nm,

– injection volume: 10 µl.

Inject reference solution (b). The test is not valid unless the resolution between the peaks due to phenindione impurity C and phenindione is not less than 6.0 and the relative standard deviation for replicate injections is not more than 2.0 per cent for phenindione peak.

Inject reference solution (a) and the test solution.

Calculate the content of $C_{15}H_{10}O_2$.

Phenindione Tablets. Page3241

Para 1

Change **to**: Phenindione Tablets contains not less than 95.0 per cent and not more than 105.0 per cent of the stated amount of phenindione, $C_{15}H_{10}O_2$.

Identification

Change **to**: A. Shake a quantity of the powdered tablets containing 0.2 g of Phenindione with 50 ml of *dichloromethane,* filter and evaporate the filtrate to dryness. On the residue, determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *phenindione IPRS* or with the reference spectrum of phenindione.

B. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with reference solution (a).

Related substances. Change **to**:
Related substances. Determine by liquid chromatography (2.4.14).

NOTE — Prepare the solutions immediately before use.

Test solution. Disperse a quantity of the powdered tablets containing 25 mg of Phenindione in *methanol* and dilute to 10.0 ml with *methanol*, mix and centrifuge. Use the supernatant liquid.

Reference solution (a). A 0.0025 per cent w/v solution of *phenindione IPRS* in *methanol*.

Reference solution (b). A 0.00375 per cent w/v solution of *phenindione impurity A IPRS* in *methanol*.

Reference solution (c). A solution containing 0.0005 per cent w/v, each of, *phenindione IPRS*, *phenindione impurity C (*phenylacetic acid*), phenindione impurity D (*benzalphthalide) and *phenindione impurity E (*phthalic acid)in *methanol*.

Reference solution (d). Dilute 1.0 ml of reference solution (a) to 10.0 ml with *methanol*.

Chromatographic system
– a stainless steel column 10 cm x 4.6 mm, packed with end-capped octadecylsilane bonded to porous silica (3.5 µm) (Such as X-bridge shield C18),
– sample temperature: 4º,
– mobile phase: A. a mixture of 10 volumes of *acetonitrile*, 10 volumes of 1.36 per cent w/v solution of *dipotassium hydrogen orthophosphate* previously adjusted to pH 3.0 with *orthophosphoric acid* and 80 volumes of *water*,
B. a mixture of 90 volumes of *acetonitrile* and 10 volumes of *water*,
– a gradient programme using the conditions given below,
– flow rate: 1.5 ml per minute,
– spectrophotometer set at 220 nm,
– injection volume: 10 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	80	20
0.5	80	20
10	50	50
13	50	50
21	30	70
22	80	20
25	80	20

Name	Relative retention time

Phenindione impurity E[1]	0.2
Phenindione impurity C[2]	0.4
Phenindione impurity A[3]	0.6
Phenindione (Retention time: about 7 minutes)	1.0
Phenindione impurity D[4]	1.7
Phenindione impurity B[5]	2.4

[1]phthalic acid,
[2]phenylacetic acid,
[3]2-hydroxy-2-phenyl-1*H*-indene-1,3(2*H*)-dione,
[4]3-benzylidene-2-benzofuran-(3*H*)-one (benzalphthalide),
[5]2'-diphenyl-1*H*,1'*H*-[2,2'-bi-indene]-1,1′,3,3'(2*H*,2'*H*)tetrone.

Inject reference solution (c). The test is not valid unless the resolution between the peaks due to phenindione impurity C and phenindione is not less than 6.0 and the resolution between the peaks due to phenindione and phenindione impurity D is not less than 8.0.

Inject reference solution (a), (b), (d) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to phenindione impurity A is not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (1.5 per cent), the area of any other secondary peak is not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent) and the sum of areas of all the secondary peaks is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (2.0 per cent). Ignore any peak with an area less than the area of the principal peak in the chromatogram obtained with reference solution (d) (0.1 per cent).

Assay. Change **to**:

Assay. Determine by liquid chromatography (2.4.14).

NOTE — Prepare the solutions immediately before use.

Solvent mixture. 2 per cent v/v solution of *glacial acetic acid* in *acetonitrile*.

Test solution. Weigh and powder 20 tablets. Disperse a quantity of powder containing 25 mg of the Phenindione in 20 ml of *0.01 M sodium hydroxide* with the aid of ultrasound, add 50 ml of the solvent mixture and dilute to 100.0 ml with the solvent mixture, mix and centrifuge. Use the supernatant liquid.

Reference solution (a). A 0.025 per cent w/v solution of *phenindione IPRS* in a mixture of 20 volumes of *0.01 M sodium hydroxide* and 80 volumes of the solvent mixture.

Reference solution (b). A solution containing 0.025 per cent w/v, each of, *phenindione IPRS* and *phenindione impurity C* (phenylacetic acid)in a mixture of 20 volumes of *0.01 M sodium hydroxide* and 80 volumes of the solvent mixture.

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with end-capped octadecylsilane bonded to porous silica (5 µm) (Such as Symmetry C18),
- sample temperature: 4°,
- mobile phase: a mixture of 60 volumes of 0.68 per cent w/v solution of *potassium dihydrogen orthophosphate* previously adjusted to pH 3.5 with *orthophosphoric acid* and 40 volumes of *acetonitrile*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 250 nm,
- injection volume: 10 µl.

Inject reference solution (b). The test is not valid unless the resolution between the peaks due to phenindione impurity C and phenindione is not less than 6.0 and the relative standard deviation for replicate injections is not more than 2.0 per cent for phenindione peak.

Inject reference solution (a) and the test solution.

Calculate the content of $C_{15}H_{10}O_2$ in the tablets.

Phenylephrine Hydrochloride. Page 3255

Para 2

Change **to**: Phenylephrine Hydrochloride contains not less than 98.0 per cent and not more than 102.0 per cent of $C_9H_{13}NO_2$, HCl, calculated on the dried basis.

Identification

Change **to**: **Identification**

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with that obtained with *phenylephrine hydrochloride IPRS* or with the reference spectrum of phenylephrine hydrochloride.

B. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with the reference solution.

C. It gives reaction (A) of chlorides (2.3.1).

Related substances. Change **to**:

Related substances. Determine by liquid chromatography (2.4.14).

Buffer solution. Dissolve 3.25 g of *1-octanesulphonic acid sodium salt monohydrate* in 1000 ml of *water*, adjust topH 2.8 with *3M orthophosphoric acid.*

Solvent mixture. 80 volumes of mobile phase A and 20 volumes of mobile phase B.

Test solution. Dissolve 50 mg of the substance under examination in the solvent mixture and dilute to 50.0 ml with the solvent mixture.

Reference solution (a). A solution containing 0.01 per cent w/v, each of, *phenylephrine hydrochloride IPRS*, *norphenylephrine hydrochloride IPRS*, *phenylephrine impurity C IPRS, phenylephrine impurity D IPRS* and *phenylephrine impurity E IPRS* in the solvent mixture. Dilute 1.0 ml of the solution to 100.0 ml with the solvent mixture.

Reference solution (b). A solution containing 0.1 per cent w/v of *phenylephrine hydrochloride IPRS*, 0.001 per cent w/v, each of, *norphenylephrine hydrochloride IPRS* and *phenylephrine impurity C IPRS* in the solvent mixture.

Chromatographic system

- a stainless steel column 5.5 cm x 4.0 mm, packed with endcapped octadecylsilane bonded to porous silica (3 µm) (Such as purospher STAR RP18e),
- column temperature: 45°,
- mobile phase: A. a mixture of 90 volumes of buffer solution and 10 volumes of *acetonitrile*,
  B. a mixture of 10 volumes of buffer solution and 90 volumes of *acetonitrile,*
- a gradient programme using the conditions given below,
- flow rate: 1.5 ml per minute,
- spectrophotometer set at 215 nm,
- injection volume: 10 µl.

Time (in min)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	93	7
3	93	7
13	70	30
14	93	7
16	93	7

Name	Relative retention time
Norphenylephrine	0.9
Phenylephrine	1.0
Phenylephrine impurity C[1]	1.3
Phenylephrine impurity D[2]	3.8
Phenylephrine impurity E[3]	4.0

[1]1-(3-Hydroxyphenyl)-2-(methylamino)ethan-1-one hydrochloride,
[2](R)-3-{2-[Benzyl(methyl)amino]-1-hydroxyethyl}phenol,
[3]2-[Benzyl(methyl)amino]-1-(3-hydroxyphenyl)ethan-1-one hydrochloride.

Inject reference solution (a) and (b).The test is not valid unless the resolution between the peaks due to norphenylephrine and phenylephrine is not less than 1.5 and between phenylephrine and phenylephrine impurity C is not less than 1.5 in the chromatogram obtained with reference solution (b) and the relative standard deviation for replicate injections is not more than 5.0 per cent for each component in the chromatogram obtained with reference solution (a).

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to norphenylephrine, phenylephrine impurity C, D and E, each of, is not more than the area of the corresponding peaks in the chromatogram obtained with reference solution (a) (0.1 per cent), the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent) and the sum of areas of all the secondary peaks is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent). Ignore any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Assay. Change **to**:
Assay. Determine by liquid chromatography (2.4.14), as described under Related substances with the following modifications.

Test solution. Dissolve 40 mg of the substance under examination in the solvent mixture and dilute to 100.0 ml with the solvent mixture.

Reference solution. A 0.04 per cent w/v solution of *phenylephrine hydrochloride IPRS* in the solvent mixture.

Inject the reference solution. The test is not valid unless the tailing factor is not more than 1.9 and the relative standard deviation for replicate injections is not more than 1.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_9H_{13}NO_2$,HCl.

Phenylephrine Eye Drops. Page 3256

Identification. A
Change **to**: A. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with the reference solution.

Related substances. Change **to**:
Related substances. Determine by liquid chromatography (2.4.14).

Buffer solution. Dissolve3.25 g of *sodium octane sulphonate monohydrate* in1000 ml of *water*, adjust to pH 2.8 with *dilute orthophosphoric acid.*

Solvent mixture. 20 volumes of mobile phase B and 80 volumes of mobile phase A.

Test solution. Dilute the eye drop, if necessary, with the solvent mixture to obtain a solution containing 0.1 per cent w/v of Phenylephrine Hydrochloride.

Reference solution (a). A 0.0002 per cent w/v solution of *phenylephrine hydrochloride IPRS* in the solvent mixture.

Reference solution (b). A solution containing 0.1 per cent w/v of *phenylephrine hydrochloride IPRS* and 0.001 per cent w/v, each of, *phenylephrine impurity C IPRS* and *phenylephrine impurity EIPRS* in the solvent mixture.

Chromatographic system
- a stainless steel column 5 cm x 4.6 mm, packed with endcapped octadecylsilane bonded to porous silica (1.8 µm) (Such as Zorbax Eclipse plus (C18),
- column temperature: 45°,
- mobile phase: A. a mixture of 90 volumes of the buffer solution and 10 volumes of *acetonitrile*,
  B. a mixture of 10 volumes of the buffer solution and 90 volumes of *acetonitrile*,
- a gradient programme using the conditions given below,
- flow rate: 1.5 ml per minute,
- spectrophotometer set at 215 nm,
- injection volume: 10 µl.

Time (in min)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	93	7
3	93	7
13	70	30
14	93	7

20	93	7

Name	Relative retention time	Correction factor
Phenylephrine (Retention time about 3 minutes)	1.0	---
Phenylephrine impurity C[1]	1.3	0.5
Phenylephrine impurity E [2]	3.7	0.5

[1]1-(3-Hydroxyphenyl)-2-(methylamino)ethan-1-one hydrochloride,
[2] 2-(benzylmethylamino)-1-(3-hydroxyphenyl)ethanone (benzylphenylephrone).

Inject reference solution (b) to identify the peaks due to phenylephrine impurity C and E.

Inject reference solution (b). The test is not valid unless the peak-to-valley ratio (Hp/Hv) is not less than 5.0, where Hp is the height above the baseline of the peak due to impurity C and Hv is the height above the baseline of the lowest point of the curve separating this peak due to phenylephrine.

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of any secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent) and the sum of areas of all the secondary peaks is not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent). Ignore any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent).

Phenylephrine Injection. Page 3257

Para 2
Change **to**: Phenylephrine Injection contains not less than 90.0 per cent and not more than 115.0 per cent of the stated amount of phenylephrine hydrochloride, $C_9H_{13}NO_2$, HCl.

Identification. A

Change **to**: A. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with the reference solution.

Related substances. Change **to**:
Related substances. Determine by liquid chromatography (2.4.14).

Test solution. Dilute a suitable volume of the injection with waterto obtain a solution containing 0.01 per cent w/v of Phenylephrine Hydrochloride.

Reference solution (a). A 0.002 per cent w/v solution of *phenylephrine hydrochloride IPRS* in *water*. Dilute 1.0 ml of the solution to 100.0 ml with *water*.

Reference solution (b). A solution containing 0.01 per cent w/v of *phenylephrine hydrochloride IPRS* and 0.0005 per cent w/v of *phenylephrine impurity F IPRS* in *water*.

Reference solution (c). Dilute 5.0 ml of reference solution (a) to 10.0 ml with *water*.

Chromatographic system
- a stainless steel column 15 cm x 4.6 mm, packed with endcapped octadecylsilane bonded to porous silica (2.6 µm) (Such as Kinetix XB-C-18),
- column temperature: 35°,
- mobile phase: A. a 0.1 per cent v/v solution of *orthophosphoric acid* in *water*,
  B. *acetonitrile,*
- a gradient programme using the conditions given below,
- flow rate: 1 ml per minute,
- spectrophotometer set at 215 nm,
- injection volume: 10 µl.

Time (in min)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	98	2
2.5	98	2
6	65	35
6.1	98	2
9	98	2

Name	Relative retention time	Correction factor
Phenylephrine	1.0	---
Phenylephrine impurity C[1]	1.2	0.36
Phenylephrine citrate adduct[2]	2.9	---

[1]1(3-Hydroxyphenyl)-2-(methylamino)ethan-1-one hydrochloride,
[2]2-Hydroxy-2-(2-{[(*R*)-2-hydroxy-2-(3-hydroxyphenyl)ethyl](methyl)amino}-2-oxoethyl)succinic acid.

Inject reference solution (a), (b) and (c).The test is not valid unless the resolution between the peak due to phenylephrine and phenylephrine impurity F is not less than 1.5 in the chromatogram obtained with reference solution (b), the relative standard deviation for replicate injections is not more than 5.0 per cent in the chromatogram obtained with reference solution (a) and the signal-to-noise ratio is not less than 10 in the chromatogram obtained with reference solution (c).

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to phenylephrine impurity C is not more than 3.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.7 per cent), the area of any peak corresponding to phenylephrine citrate adduct is not more twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.4 per cent), the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent) and the sum of areas of all the secondary peaks is not more than 6.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.3 per cent). Ignore any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Assay. Change **to**:
Assay. Determine by liquid chromatography (2.4.14), as described under Related substances with the following modifications.

Reference solution. A 0.01 per cent w/v solution of *phenylephrine hydrochloride IPRS* in *water*.

Chromatographic system
- spectrophotometer set at 273 nm.

Inject the reference solution. The test is not valid unless the tailing factor is not more than 2.5 and the relative standard deviation for replicate injections is not more than 2.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_9H_{13}NO_2$,HCl in the injection.

Phenytoin Capsules. Page 3264

Related substances. Change **to:**
Related substances. Determine by liquid chromatography (2.4.14).

Solvent mixture. Equal volumes of *water* and mobile phase B.

Test solution. Disperse a quantity of the mixed contents containing 100 mg of Phenytoin Sodium in 50 ml of the solvent mixture with the aid of mechanical shaker for 15 minutes and dilute to 100.0 ml with the solvent mixture.

Reference solution. A solution containing 0.0001 per cent w/v of *phenytoin IPRS,* 0.0005 per cent w/v of *phenytoin related compound A IPRS* and0.0009 per cent w/v of *phenytoin related compound B IPRS* in the solvent mixture.

Chromatographic system
-a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (3 µm) (Such as Inertsil ODS-3),
-mobile phase: A. a *0.05 M potassium dihydrogen phosphate*, adjusted to pH 2.5 with *orthophosphoric acid*,
B. a mixture of 40 volumes of *acetonitrile* and60 volumes of *methanol,*
-a gradient programme using the conditions given below,
-flow rate: 1 ml per minute,
-spectrophotometer set at 220 nm,
-injection volume: 20 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)

0	60	40
23	60	40
38	42	58
45	30	70
50	30	70
51	60	40
55	60	40

Name	Relative retention time
Phenytoin related compound A[1]	0.14
Phenytoin related compound B[2]	0.51
Phenytoin	1.0

[1]2,2-Diphenylglycine,
[2]2,2-Diphenyl-2-ureidoacetic acid.

Inject the reference solution. The test is not valid unless the relative standard deviation for replicate injections is not more than 5.0 per cent and the signal-to-noise ratio for the principal peak is not less than 10.0, for phenytoin peak.

Inject the reference solution and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to phenytoin related compound Ais not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (0.5 per cent), the area of any peak corresponding to phenytoin related compound Bis not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (0.9 per cent), the area of any other secondary peak is not more than twice the area of the principal peak in the chromatogram obtained with the reference solution (0.2 per cent) and the sum of the areas of all the secondary peaks is not more than 15 times the area of the principal peak in the chromatogram obtained with the reference solution (1.5 per cent).Ignore any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with the reference solution (0.05 per cent).

Assay. Change **to:**
Assay. Determine by liquid chromatography (2.4.14).

Solution A. 1 per cent v/v solution *triethylamine* in *water.*

Test solution. Weigh and mix the contents of 20 capsules. Disperse a quantity of the mixed contents containing 100 mg of Phenytoin Sodium in the mobile phase with the aid of mechanical shaker and dilute to 200.0 ml with the mobile phase.

Reference solution. A 0.05 per cent w/v solution of *phenytoin sodium IPRS* in the mobile phase.

Chromatographic system
-a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (Such as Hypersil-ODS),
-mobile phase: a mixture of 27 volumes of *methanol,* 23 volumes of *acetonitrile,* 50 volumes of *water,* 5 volumes of solution A and 1 volume of *glacial acetic acid,*
-flow rate: 1.5 ml per minute,
-spectrophotometer set at 254 nm,
-injection volume: 25 µl.

Inject the reference solution. The test is not valid unless the tailing factor is not more than 1.5 and the relative standard deviation for replicate injections is not more than 2.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{15}H_{11}N_2NaO_2$ in the capsules.

Phenytoin Tablets. Page 3267

Related substances. Change **to:**
Related substances. Determine by liquid chromatography (2.4.14).

Solvent mixture. Equal volumes of *water* and mobile phase B.

Test solution. Disperse a quantity of the powdered tablets containing 100 mg of Phenytoin Sodium in 50 ml of the solvent mixture, with the aid of mechanical shake for 15 minutes and dilute to 100.0 ml with the solvent mixture.

Reference solution. A solution containing 0.0001 per cent w/v of *phenytoin IPRS,* 0.0005 per cent w/v of *phenytoin related compound A IPRS* and0.0009 per cent w/v of *phenytoin related compound B IPRS* in the solvent mixture.

Chromatographic system
-a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (3 µm) (Such as Inertsil ODS-3),
-mobile phase: A. a *0.05 M potassium dihydrogen phosphate*, adjusted to pH 2.5 with *orthophosphoric acid*,
B. a mixture of 40 volumes of *acetonitrile* and60 volumes of *methanol,*
-a gradient programme using the conditions given below,
-flow rate: 1 ml per minute,
-spectrophotometer set at 220 nm,
-injection volume: 20 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	60	40
23	60	40
38	42	58
45	30	70
50	30	70
51	60	40
55	60	40

Name	Relative retention time
Phenytoin related compound A[1]	0.14
Phenytoin related compound B[2]	0.51
Phenytoin	1.0

[1]2,2-Diphenylglycine,
[2]2,2-Diphenyl-2-ureidoacetic acid.

Inject the reference solution. The test is not valid unless the relative standard deviation for replicate injections is not more than 5.0 per cent and the signal-to-noise ratio is not less than 10.0, for phenytoin peak.

Inject the reference solution and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to phenytoin related compound Ais not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (0.5 per cent), the area of any peak corresponding to phenytoin related compound Bis not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (0.9 per cent), the area of any other secondary peak is not more than twice the area of the principal peak in the chromatogram obtained with the reference solution (0.2 per cent) and the sum of the areas of all the secondary peaks is not more than 15 times the area of the principal peak in the chromatogram obtained with the reference solution (1.5 per cent).Ignore any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with the reference solution (0.05 per cent).

Assay. Change **to:**
Assay. Determine by liquid chromatography (2.4.14).

Solution A. 1 per cent v/v solution of *triethylamine* in *water.*

Test solution. Weigh and powder 20 tablets. Disperse a quantity of the powder containing 100 mg of Phenytoin Sodium in the mobile phase with the aid of mechanical shaker and dilute to 200.0 ml with the mobile phase.

Reference solution. A 0.05 per cent w/v solution of *phenytoin sodium IPRS* in the mobile phase.

Chromatographic system
-a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (Such as Hypersil-ODS),
-mobile phase: a mixture of 27 volumes of *menthol,* 23 volumes of *acetonitrile,* 50 volumes of *water,* 5 volumes of solution A and 1 volume of *glacial acetic acid,*
-flow rate: 1.5 ml per minute,
-spectrophotometer set at 254 nm,
-injection volume: 25 µl.

Inject the reference solution. The test is not valid unless the tailing factor is not more than 1.5 and the relative standard deviation for replicate injections is not more than 2.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{15}H_{11}N_2NaO_2$ in the tablets.

Piroxicam. Page 3295

Identification. C

Change **to**: C. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with the reference solution.

Insert before **Related substances**

Limit of piroxicam related compound B. Determine by liquid chromatography (2.4.14).

Note- Use freshly prepared solutions.

Test solution. Dissolve 0.1 g of the substance under examination in *methanol* with the aid of ultrasound and dilute to 100.0 ml with *methanol.*

Reference solution (a). A 0.0002 per cent w/v solution of *piroxicam related compound BIPRS* in *methanol.*

Reference solution (b). A solution containing 0.1 per cent w/v of *piroxicam IPRS* and 0.001 per cent w/v, each of, *piroxicam related compound BIPRS* and *piroxicam related compound GIPRS* in *methanol*.

Chromatographic system

- a stainless steel column 15 cm x 4.6 mm, octadecylsilane bonded to porous silica (3.5 µm),
- column temperature: 35º,
- sample temperature: 4º,
- mobile phase: A. a 0.1 per cent v/v solution of *orthophosphoric acid* in *water*,
- B. *acetonitrile*,
- a gradient programme using the conditions given below,
- flow rate: 1 ml per minute,
- spectrophotometer set at 340 nm,
- injection volume: 10 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0.0	65	35
2.0	65	35
6.0	5	95
6.1	65	35
11.0	65	35

Name	Relative retention time
Piroxicam Related compound B[1]	0.89
Piroxicam Related compound G[2]	0.95
Piroxicam1.0	

[1]4-Hydroxy-N-(pyridin-2-yl)-2H-benzothiazine-3-carboxamide1,1-dioxide,
[2]Methyl 4-hydroxy-2H-benzothiazine-3-carboxylate 1,1-dioxide monohydrate.

Inject reference solution (a) and (b). The test is not valid unless the resolution between the peak due to piroxicam related compound B and G is not less than 1.5 in the chromatogram obtained with reference solution (b) and the relative standard deviation for replicate injection is not more than 5.0 per cent in the chromatogram obtained with reference solution (a).

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to piroxicam related compound B is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent).

Related substances. Change **to**:

Related substances. Determine by liquid chromatography (2.4.14).

Note- Use freshly prepared solutions.

Test solution. Dissolve 0.1 g of the substance under examination in *methanol*, with the aid of ultrasound and dilute to 100.0 ml with *methanol.*

Reference solution (a). A solution containing 0.0002 per cent w/v, each of, *piroxicam IPRS, piroxicam related compound A IPRS*, *piroxicam related compound D IPRS*, *piroxicam related compound G IPRS* and *piroxicam related compound J IPRS* in *methanol*.

Reference solution (b). A 0.005 per cent w/v solution of *piroxicam IPRS* in *methanol.* Dilute 1.0 ml of the solution to 100.0 ml with *methanol*.

Chromatographic system

- a stainless steel column 15 cm x 4.6 mm, octadecylsilane bonded to porous silica (3.5 µm),
- column temperature: 30º,
- sample temperature: 4º,
- mobile phase: A. a 0.5 per cent v/v solution of *glacial acetic acid* in *water*, adjusted to pH 6.2 with *ammonium hydroxide*,
  B. *acetonitrile*,
- a gradient programme using the conditions given below,
- flow rate: 1 ml per minute,
- spectrophotometer set at 235 nm (for piroxicam, piroxicam related compound A, piroxicam related compound D and any other impurity) at 355 nm (for piroxicam related compound G and piroxicam related compound J),
- injection volume: 10 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0.0	95	5
3.0	95	5
5.0	77	23
10.0	77	23
15.0	40	60
15.1	95	5
20.0	95	5

Name	Relative retention time
Piroxicam related compound A[1]	0.35
Piroxicam related compound G[2] (as the anhydrous form)	0.86
Piroxicam1.0	
Piroxicam related compound B[3*]	1.2
Piroxicam related compound D[4]	1.36
Piroxicam related compound J[5]	1.42

[*] for peak identification only quantitated by the test for limit of piroxicam related compound B,
[1]Pyridin-2-amine,
[2]Methyl 4-hydroxy-2H-benzothiazine-3-carboxylate 1,1-dioxide monohydrate,
[3]4-Hydroxy-N-(pyridin-2-yl)-2H-benzothiazine-3-carboxamide1,1-dioxide,
[4]Methyl 2-[1,1-dioxido-3-oxobenzoisothiazol-2(3H)-yl]acetate,
[5]Methyl 4-hydroxy-2-methyl-2H-benzothiazine-3-carboxylate 1,1-dioxide.

Inject reference solution (a) and (b). The test is not valid unless the resolution between the peak due to piroxicam and piroxicam related compound G is not less than 5.0, the relative standard deviation for replicate injection is not more than 5.0 per cent for piroxicam and piroxicam related compound A, D, G, and J in the chromatogram obtained with reference solution (a) and the signal-to-noise ratio is not less than 10 in the chromatogram obtained with reference solution (b).

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to piroxicam related compound A, D, J, G, each of, is not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.2 per cent), the area of any other secondary peak is not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent).

The sum of the impurities including piroxicam related compound B (from the test for limit of piroxicam related compound B) is not more than 0.4 per cent.

Heavy metals

Change **to**: **Heavy metals** (2.3.13). 1.0 g complies with the limit test for heavy metals, Method B (20 ppm).

Water. Line 2

Change **from**: 2.0 g.

to: 1.0 g.

Assay. Change **to**:
Assay. Determine by liquid chromatography (2.4.14), as described under limit of piroxicam related compound B with the following modifications.

Test solution. Dissolve 50 mg of the substance under examination in *methanol* and dilute to 100.0 ml with *methanol*. Dilute 1.0 ml of the solution to 10.0 ml with *methanol*.

Reference solution. A 0.005 per cent w/v solution of *piroxicam IPRS* in *methanol.*

Inject the reference solution. The test is not valid unless the tailing factor is not more than 2.0 and the relative standard deviation for replicate injections is not more than 1.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{15}H_{13}N_3O_4S$.

Pitavastatin Calcium. Page 3298

Related substances. Chromatographic system, line 5 to 6
Change **from**: 1.54 per cent w/v solution of *ammonium acetate* in 1000 ml of *water*,
to: 1.54 g of *ammonium acetate* in 1000 ml of *water*,

Prazosin Hydrochloride. Page 3330

Iron. Lines 1 to 6
Change **from:** To 1.0 g add dropwise about 1.5 ml of *nitric acid*, heat cautiously on a water-bath until fumes are no longer evolved. Ignite by slowly raising the temperature from 150º to 1000º, maintaining the final temperature for 1 hour. Cool, dissolve the residue in 20 ml of *2 M hydrochloric acid*, evaporate to about 5 ml, dilute to 25 ml with *2 M hydrochloric acid…*
to: Use the residue obtained in the test for Sulphated ash, dissolve the residue in 10 ml of *2M hydrochloric acid*, evaporate to about 5 ml, dilute to 25.0 ml with *2 M hydrochloric acid…*

Heavy metals
Change **to**: 1.0 g complies with the limit test for heavy metals, Method B (20 ppm).

Water. Line 1
Change **from:** 2.0 g
to: 1.0 g

Prazosin Tablets. Page 3330

Related substances. Line 2
Change **from**: *silica gel HF254*
to: *silica gel GF254*

Line 3 & 4
Change **to**: *Solvent mixture*. 5 volumes of *diethylamine* and 95 volumes of *chloroform*.

Last para, line 1
Insert before Any secondary spot…….
"Allow the mobile phase to rise 15 cm. Dry the plate in air and examine under ultraviolet light at 254 nm."

Prednisolone. Page 3333

Identification
Change **to:** A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *prednisolone IPRS* or with the reference spectrum of prednisolone.

B. In the Assay, the principal peak in the chromatogram obtained with test solution (b) corresponds to the peak in the chromatogram obtained with reference solution (a).

Related substances. Change **to:**
Related substances. Determine by liquid chromatography (2.4.14).

NOTE- Carry out the test protected from light.

Solvent mixture. 40 volumes of *acetonitrile* and 60 volumes of *water.*

Test solution (a). Dissolve 25 mg of the substance under examination in the solvent mixture and dilute to 50.0 ml with the solvent mixture.

Test solution (b). Dilute 5.0 ml of test solution (a) to 20.0 ml with the solvent mixture.

Reference solution (a). A 0.0125 per cent w/v solution of *prednisolone IPRS* in the solvent mixture.

Reference solution (b). Dilute 2.0 ml of reference solution (a) to 50.0 ml with the solvent mixture. Further dilute 1.0 ml of the solution to 10.0 ml with the solvent mixture.

Reference solution (c). A 0.05 per cent w/v solution of *prednisolone for system suitability IPRS* (containing prednisolone impurities A, B and C) in the solvent mixture.

Reference solution (d). A 0.05 per cent w/v solution of *prednisolone for peak identification IPRS* (containing prednisolone impurities F and J) in the solvent mixture.

Chromatographic system
- a stainless steel column 15 cm x 4.6 mm, packed with end-capped octadecylsilane bonded to porous silica (3µm),
- column temperature. 40°,
- mobile phase: A. *water,*
  B. a mixture of equal volumes of *acetonitrile* and *methanol,*
- a gradient programme using the conditions given below,
- flow rate: 1 ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 10 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	60	40
14	60	40
20	20	80
25	20	80
25.1	60	40
35	60	40

Name	Relative retention time
Prednisolone impurity F[1]	0.7
Prednisolone impurity B[2]	0.9
Prednisolone (Retention time: about 12 minutes)	1.0
Prednisolone impurity A[3]	1.05
Prednisolone impurity J[4]	1.5
Prednisolone impurity C[5]	1.7

[1] 11α,17,21-trihydroxypregna-1,4-diene-3,20-dione (11-epi-prednisolone),
[2] 17,21-dihydroxypregna-1,4-diene-3,11,20-trione (prednisone),
[3] 11β,17,21-trihydroxypregn-4-ene-3,20-dione (hydrocortisone),
[4] 17,21-dihydroxypregna-1,4-diene-3,20-dione (11-deoxyprednisolone),
[5] 11β,17-dihydroxy-3,20-dioxopregna-1,4-dien-21-yl acetate (prednisolone acetate).

Inject reference solution (c) to identify the peaks due to prednisolone impurity A, B and C and reference solution (d) to identify the peaks due to prednisolone impurity F and J.

Inject reference solution (c). The test is not valid unless the peak-to-valley ratio (Hp/Hv) is not less than 3.0, where *Hp* is the height above the baseline of the peak due to prednisolone impurity A and *Hv* is the height above the baseline of the lowest point of the curve separating the peak due to prednisolone.

Inject reference solution (b) and test solution (a). In the chromatogram obtained with test solution (a), the area of any peak corresponding to prednisolone impurity A is not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent), the area of any peak corresponding to prednisolone impurity F is not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent), the area of any peak corresponding to prednisolone impurity B, C and J, each of, is not more than 3 times the area of the

principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent), the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent) and the sum of the areas of all the secondary peaks is not more than 15 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.5 per cent). Ignore any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05per cent).

Assay. Change **to:**
Assay. Determine by liquid chromatography (2.4.14), as described under Related substances.

Inject reference solution (a) and test solution (b).

Calculate the content of $C_{21}H_{28}O_5$.

Prednisolone Acetate. Page 3335

Related substances. *Reference solution (b)*
Change **to:** *Reference solution (b).* A 0.0005 per cent w/v solution of *prednisolone IPRS* in the solvent mixture.

Reference solution (c). A 0.01 per cent w/v solution of *prednisolone acetate for peak identification IPRS* (containing impurity A, B and C) in the solvent mixture.

After chromatographic system, para 1
Change **to:**

Name	Relative retention time
Prednisolone acetate impurity B[1]	0.4
Prednisolone acetate (Retention time = about 17 minutes)	1.0
Prednisolone acetate impurity A[2]	1.1
Prednisolone acetate impurity C[3]	2.0

[1]11β,17,21-trihydroxypregna-1,4-diene-3,20-dione (prednisolone),
[2]11β,17-dihydroxy-3,20-dioxopregn-4-en-21-yl acetate (hydrocortisone acetate),
[3]17-hydroxy-3,20-dioxopregna-1,4-diene-11β,21-diyl diacetate (prednisolone 11,21-diacetate),

Inject reference solution (c) to identify the peaks due to prednisolone impurity A, B and C.

Prednisone Tablets. Page 3341

Identification. B
Change **to**: B. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with the reference solution.

Prochlorperazine Maleate. Page 3358

Identification. A
Change **to**: A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *prochlorperazine maleate IPRS* or with the reference spectrum of prochlorperazine maleate.

Progesterone. Page 3363

Related substances. Change **to:**
Related substances. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve 20 mg of the substance under examination in mobile phase B and dilute to 50.0 ml with mobile phase B.

Reference solution (a). A 0.04 per cent w/v solution of *progesterone IPRS* in mobile phase B.

Reference solution (b). Dilute 1.0 ml of reference solution (a) to 100.0 ml with mobile phase B. Dilute 1.0 ml of the solution to 10.0 ml with mobile phase B.

Reference solution (c). Dissolve 2 mg of *progesterone for system suitability IPRS* (containing impurities B, C, G, I and M) in mobile phase B and dilute to 5.0 ml with mobile phase B.

Reference solution (d). Dissolve 2 mg of *progesterone for peak identification IPRS* (containing impurities D, E, J, K and L) in mobile phase B and dilute to 5.0 ml with mobile phase B.

Reference solution (e). Dissolve 10.0 mg of *progesterone for impurity H identification IPRS* in mobile phase B and dilute to 5.0 ml with mobile phase B.

Chromatographic system

- a stainless steel column 15 cm x 4.6 mm, packed with end-capped extra-dense octadecylsilane bonded to porous silica (5 µm) (Such as Kinetex XB C18),
- mobile phase: A. a mixture of equal volumes of *acetonitrile* and *water,*
  B. a mixture of 20 volumes of *water* and 80 volumes of *acetonitrile,*
- a gradient programme using the conditions given below,
- flow rate: 1ml per minute,
- spectrophotometer set at 241 nm and, for impurity H, at 286 nm,
- injection volume: 10 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	100	0
20	100	0
27	0	100
45	0	100
46	100	0
50	100	0

Name	Relative retention time
Progesterone impurity B[1]	0.60
Progesterone impurity J[2]	0.65
Progesterone impurity H[3]	0.82
Progesterone impurity K[4]	0.85
Progesterone impurity C[5]	0.93
Progesterone (Retention time: about 14 minutes)	1.0
Progesterone impurity M[6]	1.1
Progesterone impurity L[7]	1.90
Progesterone impurity I[8]	1.95
Progesterone impurity D[9] and E[10]	2.05
Progesterone impurity G[11]	2.65

[1] (20S)-20-hydroxypregn-4-en-3-one,
[2] pregna-1,4-diene-3,20-dione,
[3] pregna-4,6-diene-3,20-dione (Δ6-progesterone),
[4] pregna-4,9(11)-diene-3,20-dione,
[5](20R)-20-hydroxypregn-4-en-3-one,
[6](17α)-pregn-4-ene-3,20-dione.
[7]20-methylidene-3-oxopregn-4-en-21-al,
[8](20RS)-20-methyl-3-oxopregn-4-en-21-al,
[9](20S)-3-oxopregn-4-en-20-yl acetate,
[10](20R)-3-oxopregn-4-en-20-yl acetate,
[11]21-(cyclohexylidene) pregn-4-ene-3,20-dione,

Inject reference solution (c) to identify the peaks due to progesterone impurity B,C,G,I and M, and reference solution (d) to identify the peaks due to progesterone impurity D+E,J, Kand L, and reference solution (e) to identify the peak due to progesterone impurity H.

Inject reference solution (c). The test is not valid unless the peak-to-valley ratio is not less than 4.0, where *Hp* is the height above the baseline of the peak due to progesterone impurity M and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to progesterone.

In reference solution (e) and the test solution at 286 nm. In the chromatogram obtained with the test solution, the area of any peak corresponding to progesterone impurity H is not more than 0.0015 times the area of the principal peak in the chromatogram obtained with reference solution (e) (0.15 per cent).

Inject reference solution (b) and the test solution at 241 nm. In the chromatogram obtained with the test solution, the area of any peak corresponding to progesterone impurity I (sum of the two epimer) is not more than 6 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.6 per cent), the area of any peak corresponding to progesterone impurity C is not more than 3 times the area of the principal peak in the chromatogram obtained with

reference solution (b) (0.3 per cent), the area of any peak corresponding to progesterone impurity B is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent), sum of areas of the peaks corresponding to progesterone impurity D and E is not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent), the area of any peaks corresponding to progesterone impurity G, J, K, L and M, each of, is not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent), the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent) and the sum of the areas of all the secondary peak is not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent). Ignore any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Assay. Change **to:**
Assay. Determine by liquid chromatography (2.4.14), as described under Related substances.

Inject reference solution (a) and the test solution.

Calculate the content of $C_{21}H_{30}O_2$.

Progesterone Injection. Page 3364

Insert before **Other tests**
Related substances. Determine by liquid chromatography (2.4.14).

Test solution. Dilute a volume of injection containing 40 mg of Progesterone in *methanol* and dilute to 100.0 ml with *methanol.*

Reference solution (a). A 0.0004 per cent w/v solution of *progesterone IPRS* in *methanol.*

Reference solution (b). A 0.004 per cent w/v of *progesterone for system suitability IPRS* in *methanol.*

Reference solution (c). Dilute 1.0 ml of reference solution (a) to 10.0 ml with *methanol.*

Chromatographic system
- a stainless steel column 10 cm x 4.6 mm, packed with end-capped octadecylsilane bonded to porous silica (5 µm) (Such as Nucleosil C18 100 Å),
- mobile phase: A. *water,*
  B. *acetonitrile,*
- a gradient programme using the conditions given below,
- flow rate: 0.8ml per minute,
- spectrophotometer set at 241 nm,
- injection volume: 10 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	50	50
20	50	50
27	20	80
45	20	80
46	50	50
50	50	50

Name	Relative retention time
Progesterone impurity C[1]	0.92
Progesterone (Retention time: about 20 minutes)	1.0

[1](20R)-20-hydroxypregn-4-en-3-one,

Inject reference solution (b). The test is not valid unless the resolution between the peaks due to progesterone impurity C and progesterone is not less than 1.5.

Inject reference solution (a), (c) and the test solution. In the chromatogram obtained with the test solution, the area of any secondary peak is not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent) and the sum of the areas of all the secondary peaks is not more than the area of the principal peak

in the chromatogram obtained with reference solution (a) (1.0 per cent). Ignore any peak with an area less than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.1 per cent).

Assay. Change **to:**
Assay. Determine by liquid chromatography (2.4.14).

Test solution. Transfer a weighed quantity of injection containing 40 mg of Progesterone to a 100-ml volumetric flask, dilute to volume with *methanol.* Dilute 1.0 ml of the solution to 10.0 ml with *methanol.*

*Reference solution (a).*A 0.004 per cent w/v solution of *progesterone IPRS* in *methanol.*

*Reference solution (b).*A solution containing 0.004 per cent w/v, each of, *progesterone IPRS* and *progesterone for system suitability IPRS* in *methanol.*

Chromatographic system
- a stainless steel column 10 cm x 4.6 mm, packed with end-capped octadecylsilane bonded to porous silica (5 µm) (Such as Nucleosil C18 100 Å)
- mobile phase: a mixture of 45 volumes of *water* and 55 volumes of *acetonitrile,*
- flow rate: 1.5ml per minute,
- spectrophotometer set at 241 nm,
- injection volume: 10 µl.

Inject reference solution (b). The test is not valid unless the resolution between the peaks due to progesterone impurity C and progesterone is not less than 1.5.

Inject reference solution (a) and the test solution.

Determine weight per ml (2.4.29) of the injection and calculate the content of $C_{21}H_{30}O_2$ in the injection.

Promethazine Hydrochloride. Page 3369

Identification. B
Change **to**: B. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to peak in the chromatogram obtained with reference solution (a).

Related substances. Change **to**:
Related substances. Determine by liquid chromatography (2.4.14).

Solvent mixture. 99.9 volumes of *methanol* and 0.1volume of *triethylamine.*

Test solution. Dissolve 50 mg of the substance under examination in the solvent mixture and dilute to 100.0 ml with the solvent mixture.

Reference solution (a). A 0.0005 per cent w/v solution of *promethazine hydrochloride IPRS* in the solvent mixture.

Reference solution (b). A solution containing 0.0005 per cent w/v, each of, *promethazine hydrochloride IPRS* and *promethazine related compound B IPRS* in the solvent mixture.

Reference solution (c). Dilute 1.0 ml of reference solution (a) to 20.0 ml with the solvent mixture.

Chromatographic system
- a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (Such as Luna C18),
- mobile phase: A. a mixture of 70 volumes of a buffer solution prepared by dissolving 3.7 g of *ammonium acetate* in1000 ml of *water* and 30 volumes of *acetonitrile,*
  B. *acetonitrile*,
- a gradient programme using the conditions given below,
- flow rate: 1.4ml per minute,
- spectrophotometer set at 234 nm and 249 nm,
- injection volume: 15 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	100	0

10	60	40
18	60	40
18.1	100	0
20	100	0

Name	Relative retention time	Correction factor
Promethazine sulphoxide[1]	0.28	0.48
Desmethyl promethazine[2]	0.71	---
Promethazine	1.0	---
Promethazine related compound B[3]	1.3	---
Phenothiazine	1.7	0.5

[1]N,N-Dimethyl-1-(10H-phenothiazin-10-yl)propan-2-amine sulphoxide,
[2]N-Methyl-1-(10H-phenothiazin-10-yl)propan-2-amine,
[3]N,N-Dimethyl-2-(10H-phenothiazin-10-yl)propan-1-amine hydrochloride.

Inject reference solution (a), (b) and (c). The test is not valid unless the resolution between the peaks due to promethazine and promethazine related compound B is not less than 5.0 in the chromatogram obtained with reference solution (b), the relative standard deviation for replicate injections is not more than 3.0 per cent at 234 and 249 nm in the chromatogram obtained with reference solution (a) and the signal-to-noise ratio of the principal peak is not less than 10 at 234 and 249 nm in the chromatogram obtained with reference solution (c).

Inject reference solution (a) and the test solution at 234 nm. In the chromatogram obtained with the test solution, the area of any peak corresponding to promethazine sulphoxide is not more than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent).

Inject reference solution (a) and the test solution at 249 nm. In the chromatogram obtained with the test solution, the area of any peak corresponding to desmethyl promethazine is not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent), the area of any peak corresponding to promethazine related compound B is not more than 0.8 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.8 per cent), the area of any peak corresponding to phenothiazine is not more than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent), the area of any other secondary peak is not more than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent). Ignore any peak with an area less than 0.05 times the areas of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

The sum of all the impurities (at 234 nm and 249 nm) is not more than 1.2 per cent.

Assay. Change **to**:
Assay. Determine by liquid chromatography (2.4.14).

Solvent mixture. *0.1 M hydrochloric acid.*

Test solution. Dissolve 50.0 mg of the substance under examination in the solvent mixture, with the aid of ultrasound and dilute to 50.0 ml with the solvent mixture. Dilute 1.0 ml of the solution to 10.0 ml with the solvent mixture.

Reference solution (a). A 0.01 per cent w/v solution of *promethazine hydrochloride IPRS* in the solvent mixture.

Reference solution (b). A solution containing 0.009 per cent w/v of *promethazine hydrochloride IPRS* and 0.012 per cent w/v of *promethazine related compound B IPRS* in the solvent mixture.

Chromatographic system
- a stainless steel column 30 cm x 3.9 mm, packed with octadecylsilane bonded to porous silica (10 µm),
- mobile phase: a mixture of 85 volumes of *acetonitrile*, 27 volumes of *water* and 0.1 volume of *triethylamine,*
- flow rate: 2.5ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 20 µl.

The relative retention time with reference to promethazine, for promethazine related compound B is about 0.82. Run the chromatogram 2.5 times the retention time of the principal peak.

Inject reference solution (a) and (b). The test is not valid unless the resolution between the peaks due to promethazine and promethazine related compound B is not less than 1.5 in the chromatogram obtained with reference solution (b), the tailing factor is not more than 2.0 and the relative standard deviation for replicate injections is not more than 2.0 per cent in the chromatogram obtained with reference solution (a).

Inject reference solution (a) and the test solution.

Calculate the content of $C_{17}H_{20}N_2S$, HCl.

Promethazine Injection. Page 3369

Identification. B

Change **to:** B. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to peak in the chromatogram obtained with reference solution (a).

Related substances. Change **to**:

Related substances. Determine by liquid chromatography (2.4.14).

Solvent mixture. 0.1 per cent v/v of *triethylamine* in *methanol*.

Test solution. Dilute a suitable volume of the injection with the solvent mixture to obtain a solution containing 0.05 per cent w/v of Promethazine Hydrochloride.

Reference solution. A solution containing 0.0001 per cent w/v, each of, *promethazine hydrochloride IPRS* and *promethazine related compound B IPRS* in the solvent mixture.

Chromatographic system

- a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm),
- sample temperature: 4°,
- mobile phase: A. a mixture of 30 volumes of *acetonitrile* and 70 volumes of a buffer solution prepared by dissolving 3.7 g of *ammonium acetate* in1000 ml of *water,*
  B. *acetonitrile*,
- a gradient programme using the conditions given below,
- flow rate: 1.4ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 15 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	100	0
10	60	40
18	60	40
18.1	100	0
20	100	0

Name	Relative retention time	Correction factor
Promethazine sulphoxide[1]	0.3	3.45
Desmethyl promethazine[2]	0.7	0.91
Promethazine	1.0	---
Promethazine related compound B*	1.3	---
Phenothiazine[3]	1.7	0.43

*Process impurity is included for identification only, not to be included in total degradation product.
[1]N,N-Dimethyl-1-(10H-phenothiazin-10-yl)propan-2-amine sulfoxide.
[2]N-Methyl-1-(10H-phenothiazin-10-yl)propan-2-amine.
[3]10H-Phenothiazine.

Inject the reference solution. The test is not valid unless the resolution between the peaks due to promethazine and promethazine related compound B is not less than 5.0 and the relative standard deviation for replicate injections is not more than 2.0, for promethazine peak.

Inject the reference solution and the test solution. In the chromatogram obtained with test solution, the area of any peak corresponding to promethazine sulphoxide is not more than 13 times the area of the principal peak in the chromatogram obtained with the reference solution (2.6 per cent), the area of any peak corresponding to desmethyl promethazine and

phenothiazine, each of, is not more than the area of the principal peak in the chromatogram obtained with the reference solution (0.2 per cent), the area of any other secondary peak is not more than 0.5 times the area of the principal peak in the chromatogram obtained with the reference solution (0.1 per cent), and the sum of all the secondary peaks is not more than 14 times the area of the principal peak in the chromatogram obtained with the reference solution (2.8 per cent). Ignore any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with the reference solution (0.05 per cent).

Assay. Change **to:**
Assay. Determine by liquid chromatography (2.4.14), as described under Related substances with the following modifications.

Test solution. Dilute a suitable volume of the injection with the solvent mixture to a solution containing 0.005 per cent w/v of Promethazine Hydrochloride.

Reference solution (a). A 0.005 per cent w/v solution of *promethazine hydrochloride IPRS* in the solvent mixture.
Reference solution (b). A solution containing 0.0001 per cent w/v, each of, *promethazine hydrochloride IPRS* and *promethazine related compound B IPRS* in the solvent mixture.

The relative retention time with reference to promethazine, for promethazine related compound B is about 1.3.

Inject reference solution (a) and (b). The test is not valid unless the resolution between the peaks due to promethazine and promethazine related compound B is not less than 5.0 in the chromatogram obtained with reference solution (b), the tailing factor is not more than 2.0 and the relative standard deviation for replicate injections is not more than 1.0 per cent in the chromatogram obtained with reference solution (a).

Inject reference solution (a) and the test solution.

Calculate the content of $C_{17}H_{20}N_2S$, HCl in the injection.

Promethazine Syrup. Page 3370

Identification

Change **to**: A. Transfer an accurately measured volume of the Syrup containing about 25 mg of Promethazine Hydrochloride to a 250-ml separator and add 10 ml of *ammonia solution.* Extract the mixture with six quantities, each of, 40 ml of *chloroform,* shaking vigorously. Wash the combined chloroform layer with 25 ml of 10 per cent v/v *hydrochloric acid* and wash the acidic layer with 25 ml of *chloroform* and add the washing to the main chloroform extract. Evaporate the combined extracts on a steam bath to a volume of 5.0 to 10.0 m1, and finally evaporate, with the aid of current of air, to dryness and dissolve the residue in 2.5 ml of *carbon disulphide.* The resulting solution complies with the following test.

Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *promethazine hydrochloride IPRS*, treated in the same manner or with the reference spectrum of promethazine hydrochloride.

B. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to peak in the chromatogram obtained with reference solution (a).

Insert before **Other tests**
Related substances. Determine by liquid chromatography (2.4.14).

Solvent mixture. 0.1 per cent v/v of *triethylamine* in *methanol*.

Test solution. Transfer an accurately measured volume of the syrup containing 50 mg of Promethazine Hydrochloride to a 100-ml volumetric flask, add 50 ml of the solvent mixture, sonicate to dissolve and dilute to 100.0 ml with the solvent mixture. Centrifuge for 10 minutes and use clear supernatant.

Reference solution. A solution containing 0.0001 per cent w/v, each of, *promethazine hydrochloride IPRS* and *promethazine related compound B IPRS* in the solvent mixture.

Chromatographic system
- a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm),
- sample temperature: 4°,
- mobile phase: A. a mixture of 30 volumes of *acetonitrile* and 70 volumes of a buffer solution prepared by dissolving 3.7 g of *ammonium acetate* in1000 ml of *water,*
  B. *acetonitrile*,

- a gradient programme using the conditions given below,
- flow rate: 1.4ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 15 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	100	0
10	60	40
18	60	40
18.1	100	0
25	100	0

Name	Relative retention time	Correction factor
Promethazine sulphoxide[1]	0.3	3.85
Desmethyl promethazine[2]	0.6	---
Promethazine	1.0	---
Promethazine related compound B*	1.3	---
Phenothiazine[3]	1.5	0.45

*Process impurity included for identification only and not to bt included in total degradation product.
[1]N,N-Dimethyl-1-(10H-phenothiazin-10-yl)propan-2-amine sulphoxide.
[2]N-Methyl-1-(10H-phenothiazin-10-yl)propan-2-amine.
[3]10H-Phenothiazine.

Inject the reference solution. The test is not valid unless the resolution between the peaks due to promethazine and promethazine related compound B is not less than 5.0 and the relative standard deviation for replicate injections is not more than 5.0 per cent for promethazine peak.

Inject the reference solution and the test solution. In the chromatogram obtained with test solution, the area of any peak corresponding to promethazine sulphoxide is not more than 5 times the area of the principal peak in the chromatogram obtained with the reference solution (1.0 per cent), the area of any peak corresponding to desmethyl promethazine and phenothiazine, each of, is not more than the area of the principal peak in the chromatogram obtained with the reference solution (0.2 per cent) and the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with the reference solution (0.2 per cent). Ignore any peak with an area less than 0.25 times the areas of the principal peak in the chromatogram obtained with the reference solution (0.05 per cent).

Assay. Change **to:**
Assay. Determine by liquid chromatography (2.4.14), as described under Related substances with the following modifications.

Test solution. Transfer an accurately measured volume of the syrup containing 5 mg of Promethazine Hydrochloride to a 100-ml volumetric flask, add 40 ml of the solvent mixture, sonicate to dissolve and dilute to 100.0 ml with the solvent mixture. Centrifuge for 10 minutes and use clear supernatant

Reference solution (a). A 0.005 per cent w/v solution of *promethazine hydrochloride IPRS* in the solvent mixture.

Reference solution (b). A solution containing 0.0001 per cent w/v, each of, *promethazine hydrochloride IPRS* and *promethazine related compound B IPRS* in the solvent mixture.

The relative retention time with reference to promethazine, for promethazine related compound B is about 1.3.

Inject reference solution (a) and (b). The test is not valid unless the resolution between the peaks due to promethazine and promethazine related compound B is not less than 5.0 in the chromatogram obtained with reference solution (b), the tailing factor is not more than 2.0 and the relative standard deviation for replicate injections is not more than 1.0 per cent in the chromatogram obtained with reference solution (a).

Inject reference solution (a) and the test solution.

Calculate the content of $C_{17}H_{20}N_2S$, HCl in the syrup.

Identification. B
Change **to:** B. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with reference solution (a).

Insert before **Related substances**
Dissolution (2.5.2).
Apparatus No. 1 (Basket),
Medium. 900 ml of *0.01 M hydrochloric acid*,
Speed and time. 100 rpm and 45 minutes.

Withdraw a suitable volume of the medium and filter. Measure the absorbance of the filtrate, dilute suitably, if necessary, with the medium, at the maximum at about249 nm (2.4.7). Calculate the content of $C_{17}H_{20}N_2S$, HCl in the medium from the absorbance obtained from a solution of known concentration of *promethazine hydrochloride IPRS* in the dissolution medium.

Q. Not less than 75 per cent of the stated amount of $C_{17}H_{20}N_2S$, HCl.

Related substances. Change **to:**
Related substances. Determine by liquid chromatography (2.4.14).

Solvent mixture. 99.9 volumes of *methanol* and 0.1volume of *triethylamine.*

Test solution. Disperse a quantity of powdered tablets containing 50 mg of Promethazine Hydrochloride, in the solvent mixture, shake for 5 minutes and dilute to 100.0 ml with the solvent mixture.

Reference solution (a). A 0.0005 per cent w/v solution of *promethazine hydrochloride IPRS* in the solvent mixture.

Reference solution (b). A solution containing 0.0005 per cent w/v, each of, *promethazine hydrochloride IPRS* and *promethazine related compound B IPRS* in the solvent mixture.

Reference solution (c). Dilute 1.0 ml of reference solution (a) to 20.0 ml with the solvent mixture.

Chromatographic system
- a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm),
- mobile phase: A. a mixture of 30 volumes of *acetonitrile* and 70 volumes of a buffer solution prepared by dissolving 3.7 g of *ammonium acetate* in1000 ml of *water,*
  B. *acetonitrile*,
- a gradient programme using the conditions given below,
- flow rate: 1.4ml per minute,
- spectrophotometer set at 234 nm and 249 nm,
- injection volume: 15 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	100	0
10	60	40
18	60	40
18.1	100	0
20	100	0
25	100	0

Name	Relative retention time	Correction factor
Promethazine sulphoxide[1]	0.28	0.48
Desmethyl promethazine[2]	0.71	---
Promethazine	1.0	---
Promethazine related compound B[3*]	1.3	---
Phenothiazine	1.7	0.5

[*]This is a process impurity and is included for identification only. It is not to be reported and not to be included in the total degradation products.
[1]N,N-Dimethyl-1-(10H-phenothiazin-10-yl)propan-2-amine sulphoxide.
[2]N-Methyl-1-(10H-phenothiazin-10-yl)propan-2-amine.
[3]N,N-Dimethyl-2-(10H-phenothiazin-10-yl)propan-1-amine hydrochloride.

Inject reference solution (a), (b) and (c). The test is not valid unless the resolution between the peaks due to promethazine and promethazine related compound B is not less than 5.0 in the chromatogram obtained with reference solution (b), the relative standard deviation for replicate injections is not more than 3.0 per cent at 234 and 249 nm in the chromatogram obtained with reference solution (a) and the signal-to-noise ratio of the principal peak at 234 nm and 249 nm is not less than 10 in the chromatogram obtained with reference solution (c).

Inject reference solution (a) and the test solution at 234 nm. In the chromatogram obtained with test solution, the area of any peak corresponding to promethazine sulphoxide is not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent).

Inject reference solution (a) and the test solution at 249 nm. In the chromatogram obtained with test solution, the area of any peak corresponding to desmethyl promethazine and promethazine, each of, is not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent), the area of any other secondary peak is not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent). Ignore any peak with an area less than 0.05 times the areas of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

The sum of all the impurities (at 234 nm and 249 nm) is not more than 1.0 per cent.

Assay. Change **to:**
Assay. Determine by liquid chromatography (2.4.14).

Solvent mixture. *0.1 M* of *hydrochloric acid*.

Test solution. Weigh and powder 20 tablets. Disperse a quantity of the powder containing 50.0 mg of Promethazine Hydrochloride in the solvent mixture, with the aid of ultrasound for 20 minutes with intermittent shaking and dilute to 50.0 ml with the solvent mixture. Dilute 1.0 ml of the solution to 10.0 ml with the solvent mixture.

Reference solution (a). A 0.01 per cent w/v solution of *promethazine hydrochloride IPRS* in the solvent mixture.

Reference solution (b). A solution containing 0.009 per cent w/v of *promethazine hydrochloride IPRS* and 0.012 per cent w/v of *promethazine related compound B IPRS* in the solvent mixture.

Chromatographic system
- a stainless steel column 30 cm x 3.9 mm, packed with octadecylsilane bonded to porous silica (10 µm),
- mobile phase: mixture of 85 volumes of *acetonitrile*, 27 volumes of *water* and 0.1 volume of *triethylamine,*
- flow rate: 2.5ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 20 µl.

The relative retention time with reference to promethazine, for promethazine related compound B is about 0.82.

Inject reference solution (a) and (b). The test is not valid unless the resolution between the peaks due to promethazine and promethazine related compound B is not less than 1.5 in the chromatogram obtained with reference solution (b), the tailing factor is not more than 1.5 and the relative standard deviation for replicate injections is not more than 2.0 per cent in the chromatogram obtained with reference solution (a).

Inject reference solution (a) and the test solution.

Calculate the content of $C_{17}H_{20}N_2S$, HCl in the tablets.

Propranolol Hydrochloride. Page 3377

Para 2
Change **to**: Propranolol Hydrochloride contains not less than 98.0 per cent and not more than 102.0 per cent of $C_{16}H_{21}NO_2$, HCl, calculated on the dried basis.

Identification. B

Change **to**: B. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to peak in the chromatogram obtained with the reference solution.

Related substances. Change **to**:
Related substances. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve 0.1 g of the substance under examination in the mobile phase and dilute to 50.0 ml with the mobile phase.

Reference solution (a). A 0.0002 per cent w/v solution of *propranolol hydrochloride IPRS* in the mobile phase.

Reference solution (b). A solution containing 0.2 per cent w/v of *propranolol hydrochloride IPRS* and0.0002 per cent w/v of *propranolol related compound A IPRS* in the mobile phase.

Reference solution (c). Dilute 5.0 ml of reference solution (a) to 10.0 ml with the mobile phase.

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (Such as Zorbox Eclipse XDB-C18),
- mobile phase: dissolve 0.31 g of *tetrabutylammonium dihydrogen phosphate* and 1.6 g of *sodium lauryl sulphate* in a mixture of 1 ml of *sulphuric acid*, 450 ml of *water* and 550 ml of *acetonitrile*, adjusted to pH 3.3 with *2 M sodium hydroxide,*
- flow rate: 1.8 ml per minute,
- spectrophotometer set at 292 nm,
- injection volume: 20 µl.

Name	Relative retention time	Correction factor
Propranolol related compound A[1]	0.6	0.71
Propranolol	1.0	---
Propranolol dimer[2]	4.8	0.77
Dinaphthyl glycerol[3]	5.7	0.53

[1]3-(naphthalen-1-yloxy)propane-1,2-diol,
[2]3,3′-(isopropylazanediyl)bis[1-(naphthalen-1-yloxy)propan-2-ol,
[3]1,3-bis[naphthalen-1-yloxy]propan-2-ol.

Inject reference solution (a), (b) and (c). The test is not valid unless the resolution between the peaks due to propranolol and propranolol related compound A is not less than 3.0 in the chromatogram obtained with reference solution (b), the relative standard deviation for replicate injections is not more than 5.0 per cent in the chromatogram obtained with reference solution (a) and signal-to-noise ratio for the principal peak is not less than 10 in the chromatogram obtained with reference solution (c).

Inject reference solution (a) and the test solution. Run the chromatogram 7 times the retention time of the principal peak. In the chromatogram obtained with the test solution, the area of any peak corresponding to propranolol related compound A, propranolol dimer and dinaphthyl glycerol, each of, is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent), the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent) and the sum of the areas of all the secondary peaks is not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.4 per cent). Ignore any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05per cent).

Assay. Change **to**:
Assay. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve 50 mg of the substance under examination in the mobile phase and dilute to 25.0 ml with the mobile phase. Dilute 5.0 ml of the solution to 50.0 ml with the mobile phase.

Reference solution. A 0.02 per cent w/v solution of *propranolol hydrochloride IPRS* in the mobile phase.

Use the chromatographic system as described under Related substances.

Inject the reference solution. The test is not valid unless the tailing factor is not more than 2.0 and the relative standard deviation for replicate injections is not more than 1.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{16}H_{21}NO_2$.HCl.

Propranolol Prolonged-release Capsules. Page 3378

Para 4

Change **to**: Propranolol Prolonged-release Capsules contains not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of propranolol hydrochloride, $C_{16}H_{21}NO_2$,HCl.

Identification

Change **to:** A. Transfer the mixed contents of the capsules containing 160 mg of Propranolol Hydrochloride to a glass mortar. Add 5 ml of *water* and triturate the mixture with a glass pestle. Transfer the suspension to a centrifuge tube with the aid of 10 ml of *water.* Add 1 ml of *1 M sodium hydroxide*, add 15 ml of *ether* and shake by mechanical means for 5 minutes. Centrifuge the mixture and transfer as much of the ether layer as possible to a second centrifuge tube. Add 0.1 ml of *hydrochloric acid* to the ether extract and shake. Centrifuge and discard the ether layer. Add 15 ml of *ether* to the precipitate and shake by mechanical means for 5 minutes. Centrifuge and discard the ether layer. Dry the residue in vacuum at 45º for 30 minutes.

On the residue, determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *propranolol hydrochloride IPRS* treated in the same manner or with the reference spectrum of propranolol.

B. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with the reference solution.

Related substances. Change **to**:

Related substances. Determine by liquid chromatography (2.4.14).

NOTE- Protect the solutions from light.

Test solution. Disperse a quantity of the mixed contents of the capsules containing 0.1 g of Propranolol Hydrochloride in the mobile phase, with the aid of ultrasound for 15 minutes and dilute to 50.0 ml with the mobile phase. Centrifuge a portion of the solution for 10 minutes and pass the solution through a suitable filter.

Reference solution (a). A 0.0004 per cent w/v solution of *propranolol hydrochloride IPRS* in the mobile phase.

Reference solution (b). A solution containing 0.2 per cent w/v of *propranolol hydrochloride IPRS* and0.0002 per cent w/v of *propranolol related compound A IPRS* in the mobile phase.

Reference solution (c). Dilute 5.0 ml of reference solution (a) to 25.0 ml with the mobile phase.

Chromatographic system

- a stainless steel column 25 cm x4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (Such as Zorbax Eclipse XDB C18),
- mobile phase: dissolve 0.31 g of *tetrabutylammonium dihydrogen phosphate* and 1.6 g of *sodium lauryl sulphate* in a mixture of 1 ml of *sulphuric acid*, 450 ml of *water* and 550 ml of *acetonitrile*, adjusted to pH 3.3 with *2 M sodium hydroxide,*
- -flow rate: 1.8 ml per minute,
- spectrophotometer set at 292 nm,
- injection volume: 20 µl.

Name	Relative retention time	Correction factor
Propranolol related compound A[1]	0.6	0.71
Propranolol	1.0	---
Propranolol dimer[2]	4.7	0.71
Dinaphthyl glycerol[3]	6.1	0.53

[1]3-(naphthalen-1-yloxy)propane-1,2-diol,
[2]3,3′-(isopropylazanediyl)bis[1-(naphthalen-1-yloxy)propan-2-ol,
[3]1,3-bis[naphthalen-1-yloxy]propan-2-ol.

Inject reference solution (a), (b) and (c). The test is not valid unless the resolution between the peaks due to propranolol and propranolol related compound Ais not less than 3in the chromatogram obtained with reference solution (b), the relative standard deviation for replicate injections is not more than 5.0 per cent in the chromatogram obtained with reference solution (a) and the signal-to-noise ratio for the principal peak is not less than 10 in the chromatogram obtained with reference solution (c).

Inject reference solution (a) and the test solution. Run the chromatogram 11 times the retention time of the principal peak. The area of any peak corresponding to propranolol related compound A, propranolol dimer and dinaphthyl glycerol, each

of, is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent), the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent) and the sum of the areas of all the secondary peaks is not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.8 per cent). Ignore any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with the reference solution (a) (0.1per cent).

Assay. Change **to:**
Assay. Determine by liquid chromatography (2.4.14).

*Solvent mixture.*35 volumes of *acetonitrile* and 65 volumes of *water.*

Test solution. Weigh a quantity of the mixed contents of 20 capsules containing 0.1 g of Propranolol Hydrochloride and transfer to a 500-ml volumetric flask, add 300 ml of *methanol* and swirl by mechanical means for 2 hours. Allow standing for 16 hours then sonicating for 30 minutes and swirl for 30 minutes, dilute to volume with *methanol.* Centrifuge a portion of the solution. Dilute 5.0 ml supernatant liquid to 50.0 ml with solvent mixture.

Reference solution. A 0.02 per cent w/v solution of *propranolol hydrochloride IPRS* in *methanol.* Dilute 5.0 ml of the solution to 50.0 ml with the solvent mixture.

Chromatographic system
- a stainless steel column 15 cm x 4.0 mm, packed with octadecylsilane bonded to porous silica (5 µm)(Such as Spherisorb ODS),
- mobile phase: a mixture of 35 volumes of *acetonitrile* and 65 volumes of 0.68 per cent w/v solution of *potassium dihydrogen phosphate* in *water,*
-flow rate: 2 ml per minute,
- spectrophotometer set at 220 nm,
- injection volume: 20 µl.

Inject the reference solution. The test is not valid unless the column efficiency is not less than 1000 theoretical plates, the tailing factor is not more than 3.0 and the relative standard deviation for replicate injections is not more than 2.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{16}H_{21}NO_2$.HCl in the capsules.

Propranolol Injection. Page 3379

Identification. B
Change **to**: B. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to peak in the chromatogram obtained with reference solution (b).

Related substances. Change **to**:
Related substances. Determine by liquid chromatography (2.4.14).

Test solution. Dilute a volume of the injection with *acetonitrile,* if necessary, to obtain a solution containing about 0.1 per cent w/v of Propranolol Hydrochloride.

Reference solution (a). A 0.0004 per cent w/v solution of *propranolol hydrochloride IPRS* in the mobile phase.

Reference solution (b). A solution containing 0.1 per cent w/v of *propranolol hydrochloride IPRS* and0.0004 per cent w/v of *propranolol related compound A IPRS* in the mobile phase.

Chromatographic system
- a stainless steel column 25 cm x4.6 mm, packed with end-capped octadecylsilane bonded to porous silica (5 µm) (Such as Hypersil ODS),
- mobile phase: dissolve 0.31 g of *tetrabutylammonium dihydrogen phosphate* and 1.6 g of *sodium lauryl sulphate* in a mixture of 1 ml of *sulphuric acid,* 450 ml of *water* and 550 ml of *acetonitrile*, adjusted to pH 3.3 with *2 M sodium hydroxide,*
-flow rate: 1.8 ml per minute,
- spectrophotometer set at 292 nm,
- injection volume: 40 µl.

Name	Relative retention time	Correction

		factor
Propranolol related compound A[1]	0.6	0.71
Propranolol	1.0	---
Propranolol dimer[2]	4.5	0.71
Dinaphthyl glycerol[3]	6.2	0.53

[1]3-(naphthalen-1-yloxy)propane-1,2-diol,
[2]3,3′-(isopropylazanediyl)bis[1-(naphthalen-1-yloxy)propan-2-ol,
[3]1,3-bis[naphthalen-1-yloxy]propan-2-ol.

Inject reference solution (b). The test is not valid unless the resolution between the peaks due to propranolol and propranolol related compound A is not less than 1.5.

Inject reference solution (a) and the test solution. Run the chromatogram 7 times the retention time of the principal peak. The area of any peak corresponding to propranolol related compound A, propranolol dimer and dinaphthyl glycerol, each of, is not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent), the area of any other secondary peak is not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent) and the sum of the areas of all the secondary peaks is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.8 per cent). Ignore any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1per cent).

Assay. Change **to**:
Assay. Determine by liquid chromatography (2.4.14).

Test solution. Dilute a volume of injection with *methanol* to obtain a solution containing about 0.02 per cent w/v of Propranolol Hydrochloride.

Reference solution (a). A 0.1per cent w/v solution of *propranolol hydrochloride IPRS* in *methanol.*

Reference solution (b). Dilute 2.0 ml of reference solution (a) to 10.0 ml with *methanol.*

Reference solution (c). A 0.025 per cent w/v solution of *procainamide hydrochloride IPRS* in *methanol.*

Reference solution (d). Dilute 5.0 ml, each of, reference solution (a) and reference solution (c) to 25.0 ml with *methanol.*

Chromatographic system
- a stainless steel column 25 cm x4.6 mm, packed with octylsilane bonded to porous silica (5 µm),
- mobile phase: dissolve 2 g of *sodium lauryl sulphate* in 72 ml of *0.15 M orthophosphoric acid,* add 360 ml of *acetonitrile* and 360 ml of *methanol* and dilute in 1000 ml with *water,*
-flow rate: 1.5 ml per minute,
- spectrophotometer set at 290 nm,
- injection volume: 20 µl.

The relative retention time with reference to propranolol, for procainamide is about 0.6.

Inject reference solution (b) and (d). The test is not valid unless the resolution between the peaks due to procainamide and propranolol is not less than 2.0 in the chromatogram obtained with reference solution (d), the tailing factor is not more than 3.0 and the relative standard deviation for replicate injections is not more than 2.0 per cent in the chromatogram obtained with reference solution (b).

Inject reference solution (b) and the test solution.

Calculate the content of $C_{16}H_{21}NO_2$.HCl in the injection.

Propranolol Tablets. Page 3380

Para 2
Change **to**: Propranolol Tablets contains not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of propranolol hydrochloride, $C_{16}H_{21}NO_2$, HCl.

Identification. B
Change **to**: B. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to peak in the chromatogram obtained with the reference solution.

Related substances. Change **to:**
Related substances. Determine by liquid chromatography (2.4.14).

Test solution. Disperse a quantity of the powdered tablets containing 0.1 g of Propranolol Hydrochloride in the mobile phase with the aid of ultrasound and dilute to 50.0 ml with the mobile phase. Centrifuge a portion of the solution for 10 minutes and pass the solution through a suitable filter.

Reference solution (a). A 0.0004 per cent w/v solution to *propranolol hydrochloride IPRS* in the mobile phase.

Reference solution (b). A solution containing 0.2 per cent w/v of *propranolol hydrochloride IPRS* and0.0002 per cent w/v of *propranolol related compound A IPRS* in the mobile phase.

Reference solution (c). Dilute 5.0 ml of reference solution (a) to 20.0 ml with the mobile phase.

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (Such as Zorbox Eclipse XDB-C18),
- mobile phase: dissolve 0.31 g of *tetrabutylammonium dihydrogen phosphate* and 1.6 g of *sodium lauryl sulphate* in a mixture of 1 ml of *sulphuric acid,* 450 ml of *water* and 550 ml of *acetonitrile*, adjusted to pH 3.3 with *2 M sodium hydroxide,*
- flow rate: 1.8 ml per minute,
- spectrophotometer set at 292 nm,
- injection volume: 20 µl.

Name	Relative retention time	Correction factor
Propranolol related compound A[1]	0.6	0.71
Propranolol	1.0	---
Propranolol dimer[2]	4.7	0.71
Dinaphthyl glycerol[3]	6.1	0.53

[1]3-(naphthalen-1-yloxy)propane-1,2-diol,
[2]3,3′-(isopropylazanediyl)bis[1-(naphthalen-1-yloxy)propan-2-ol,
[3]1,3-bis[naphthalen-1-yloxy]propan-2-ol.

Inject reference solution (a), (b) and (c). The test is not valid unless the resolution between the peaks due to propranolol and propranolol related compound Ais not less than 3.0 in the chromatogram obtained with reference solution (b), the relative standard deviation for replicate injection is not more 5.0 per cent in the chromatogram obtained with reference solution (a) and the signal-to-noise ratio is not less than 10 in the chromatogram obtained with reference solution (c).

Inject reference solution (a) and the test solution. Run the chromatogram 11 times the retention time of the principal peak. The area of any peak corresponding to propranolol related compound A, propranolol dimer and dinaphthyl glycerol, each of, is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent), the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent) and the sum of the areas of all the secondary peaks is not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent). Ignore any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1per cent).

Assay. Change **to**:
Assay. Determine by liquid chromatography (2.4.14).

Test solution. Weigh and powder 20 tablets. Disperse a quantity of the powder containing 0.1 g of Propranolol Hydrochloride in the mobile phase, with the aid of ultrasound and dilute to 100.0 ml with the mobile phase. Centrifuge a portion of the solution for 10 minutes and pass the solution through a suitable filter. Dilute 5.0 ml of the filtrate to 25.0 ml with the mobile phase.

Reference solution. A 0.02 per cent w/v solution of *propranolol hydrochloride IPRS* in the mobile phase.

Use the chromatographic system as described under Related substances.

NOTE- Run the chromatogram 11 times the retention time of the principal peak.

Inject the reference solution. The test is not valid unless the tailing factor is not more than 2.0 and the relative standard deviation for replicate injections is not more than 1.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{16}H_{21}NO_2$.HCl in the tablets.

Pyrazinamide Tablets. Page 3400

Insert after **Identification**

Test A may be omitted if tests B and C are carried out. Tests B and C may be omitted if test A is carried out.

Quinapril and Hydrochlorothiazide Tablets. Page 3414

Related substances. *Test solution*

Change **to**: *Test solution*. Disperse a quantity of the powdered tablets containing 62.5 mg of hydrochlorothiazide in 50 ml of the solvent mixture, with the aid of ultrasound for 10 minutes. Add 50 ml of *acetonitrile*, mix with the aid of ultrasound for 15 minutes with occasional shaking and dilute to 250.0 ml with the solvent mixture. Dilute a suitable volume of the solution, if necessary, with the solvent mixture to obtain a solution containing 0.025 per cent w/v of hydrochlorothiazide and 0.02 per cent w/v of Quinapril.

Reference solution

Change **to**: *Reference solution*. A solution containing 0.004 per cent w/v, each of, *quinapril hydrochloride IPRS* equivalent to quinapril, *quinapril related compound A IPRS*, *quinapril related compound B IPRS* and 0.005 per cent w/v, each of, *hydrochlorothiazide IPRS* and *benzothiadiazine related compound A IPRS* in the solvent mixture. Dilute 1.0 ml of the solution to 100.0 ml with the solvent mixture.

Quinidine Sulphate. Page 3416

Identification. C

Change **to**: C. Dissolve 0.1 g in 3 ml of *dilute sulphuric acid* and dilute to 100 ml with *water*. When examined in ultraviolet light at 366 nm; an intense blue fluorescence is produced, which disappears almost completely on the addition of 1 ml of *hydrochloric acid*.

Quinine Bisulphate Tablets. Page 3421

Identification A. *Reference solution*

Change **to**: *Reference solution (a).* A 1.0 per cent w/v solution of *quinine sulphate IPRS* in a mixture of 2 volumes of *chloroform* and 1 volumes of *ethanol (95 per cent)*.

Reference solution (b). A solution containing 1.0 per cent w/v, each of, *quinidine sulphate IPRS* and *quinine sulphate IPRS* in a mixture of 2 volumes of *chloroform* and 1 volumes of *ethanol (95 per cent)*.

Last para, last line

Change **from**:……reference solution.

to:…….. reference solution (a). The test is not valid unless the chromatogram obtained with reference solution (b) shows two clearly separated spots.

Quinine Dihydrochloride Injection. Page 3423

Assay. Line 6 and 7

Change **from**: Remove the chloroform from the combined extracts, dissolve the residue in 50 ml of *anhydrous glacial acetic acid* and add 20 ml of *acetic anhydride*.

to: Filter the chloroform layer through *anhydrous sodium sulphate*, wash with *chloroform*. Evaporate the combined filtrate on a water-bath. Dissolve the residue in 50 ml of *anhydrous glacial acetic acid* and add 20 ml of *acetic anhydride*.

Quinine Sulphate. Page 3425

Identification. C

Change **to**: C. Dissolve 0.1 g in 3 ml of *dilute sulphuric acid* and dilute to 100 ml with *water*. When examined in ultraviolet light at 366 nm; an intense blue fluorescence is produced, which disappears almost completely on the addition of 1 ml of *hydrochloric acid*.

Quinine Tablets. Page 3426

Identification A. *Reference solution*

Change **to**: *Reference solution (a).* A 1.0 per cent w/v solution of *quinine sulphate IPRS* in a mixture of 2 volumes of *chloroform* and 1 volumes of *ethanol (95 per cent)*.

Reference solution (b). A solution containing 1.0 per cent w/v, each of *quinidine sulphate IPRS* and *quinine sulphate IPRS* in a mixture of 2 volumes of *chloroform* and 1 volumes of *ethanol (95 per cent)*.

Last para, last line

Change **from**:.……reference solution.
to:……..reference solution (a). The test is not valid unless the chromatogram obtained with reference solution (b) shows two clearly separated spots.

Dissolution.Line 7 and 10
Change **from**: $C_{20}H_{24}N_2O_2$, H_2SO_4, $2H_2O$
to: $(C_{20}H_{24}N_2O_2)_2$, H_2SO_4, $2H_2O$

Ramipril. Page 3455

Related substances. Change **to:**
Related substances. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve 20 mg of the substance under examination in mobile phase A and dilute to 20.0 ml with mobile phase A.

Reference solution (a). A0.0005 per cent w/v solution of *ramipril IPRS* in mobile phase B.

Reference solution (b). A solution containing 0.008 per cent w/v, each of, *ramipril impurity A IPRS, ramipril impurity B IPRS, ramipril impurity C IPRS* and *ramipril impurity D IPRS,* in mobile phase A. To 1.0 ml of the solution, add 5 ml of reference solution (a) and dilute to 10.0 ml with mobile phase B.

Reference solution (c). Dilute 1.0 ml of reference solution (a) to 10.0 ml with mobile phase B.

Chromatographic system
- a stainless steel column 25 cm x 4.0 mm, packed with end-capped octadecylsilane bonded to porous silica (3 µm),
- column temperature. 65°,
- mobile phase: A. dissolve 2.0 g of *sodium perchlorate* in a mixture of 0.5 ml of *triethylamine* and 800 ml of *water,* adjusted to pH 3.6 with *orthophosphoric acid* and add 200 ml of *acetonitrile,*
  B. dissolve 2.0 g of *sodium perchlorate* in a mixture of 0.5 ml of *triethylamine* and 300 ml of *water,* adjusted to pH 2.6 with *orthophosphoric acid* and add 700 ml of *acetonitrile,*
- a gradient programme using the conditions given below,
- flow rate: 1 ml per minute,
- spectrophotometer set at 210 nm,
- injection volume: 10 µl.

Time (min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	90	10
6	90	10
7	75	25
20	65	35
30	25	75
50	25	75
51	90	10
55	90	10

Name	Relative retention time	Correction factor
Ramipril impurity A[1]	0.8	---
Ramipril (Retention time: about 18 minutes)	1.0	---
Ramipril impurity B[2]	1.3	---

Ramipril impurity C[3]	1.5	2.4
Ramipril impurity D[4]	1.7	---

[1](2*S*,3a*S*,6a*S*)-1-[(2*S*)-2-[[(2*S*)-1-methoxy-1-oxo-4-phenylbutan-2-yl]amino]propanoyl]octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid (*ramipril* methyl ester),
[2](2*S*,3a*S*,6a*S*)-1-[(2*S*)-2-[[(2*S*)-1-oxo-4-phenyl-1-[(propan2-yl)oxy]butan-2-yl]amino]propanoyl]octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid (*ramipril* isopropyl ester),
[3](2*S*,3a*S*,6a*S*)-1-[(2*S*)-2-[[(2*S*)-4-cyclohexyl-1-ethoxy-1oxobutan-2-yl]amino]propanoyl]octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid (hexahydroramipril),
[4]ethyl(2S)-2-[(3S,5aS,8aS,9aS)-3-methyl-1,4-dioxodecahydro-2H-cyclopenta[4,5]pyrrolo[1,2-a]pyrazin-2-yl]-4-phenylbutanoate(ramipril diketopiperazine),

Inject reference solution (b) to identify the peaks due to ramipril impurity A, B, C and D.

Inject reference solution (a), (b), (c) and the test solution. The test is not valid unless the resolution between the peaks due to ramipril impurity A and ramipril is not less than 3.0 in the chromatogram obtained with reference solution (b), signal-to-noise ratio for the principal peak is not less than 3in the chromatogram obtained with reference solution (c) and the tailing factor is not more than 10.0 in the chromatogram obtained with reference solution (a).

Inject reference solution (a), (c) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to ramipril impurity A, ramipril impurity B, ramipril impurity C and ramiptil impurity D, each of, is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent), the area of any other secondary peak is not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent) and the sum of the areas of all the secondary peaks is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent). Ignore any peak with an area less than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Ramipril Capsules. Page 3456

Insert before **Uniformity of content**

Related substances. Determine by liquid chromatography (2.4.14).

Test solution. Disperse a quantity of the mixed contents of capsules containing 25 mg of Ramipril in the mobile phase, with the aid of ultrasound for 10 minutes with intermittent shaking and dilute to 50.0 ml with the mobile phase, filter.

Reference solution (a). A0.0025 per cent w/v solution of *ramipril IPRS* in the mobile phase.

Reference solution (b). Dilute 5.0 ml of reference solution (a) to 25.0 ml with the mobile phase.

Reference solution (c). A solution containing 0.05 per cent w/v of *ramipril IPRS* and0.0005 per cent w/v, each of, *ramipril impurity A IPRS, ramipril impurity D IPRS* and *ramipril impurity K IPRS,* in the mobile phase.

Chromatographic system

- a stainless steel column 12.5 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (Such as Nucleosil 100-C18),
- mobile phase: a mixture of 68 volumes of a buffer solution containing 1.4 per cent w/v of *sodium perchlorate* and 0.58 per cent w/v of *orthophosphoric acid*, adjusted to pH 3.9 with *triethylamine* and 35 volumes of *acetonitrile,* adjust the pH 2.6 with *orthophosphoric acid*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 210 nm,
- injection volume: 15 µl.

Name	Relative retention time
Ramipril impurity E[1]	0.3
Ramipril impurity K[2]	0.5
Ramipril impurity A[3]	0.7
Ramipril(Retention time: about 10 minutes)	1.0
Ramipril impurity D[4]	2.6

[1](2S,3aS,6aS)-1-[(2S)-2-[[(1S)-1-carboxy-3-phenylpropyl]amino]propanoyl]octahydrocyclopenta[b]pyrrole-2-carboxylic acid (ramiprilat),
[2](2S)-2-[(3S,5aS,8aS,9aS)-3-methyl-1,4-dioxodecahydro-2H-cyclopenta[4,5]pyrrolo[1,2-a]pyrazin-2-yl]-4-phenylbutanoic acid (ramiprilate diketopiperazine),

[3](2S,3aS,6aS)-1-[(2S)-2-[[(2S)-1-methoxy-1-oxo-4-phenylbutan-2-yl]amino]propanoyl]octahydrocyclopenta[b]pyrrole-2-carboxylicacid (ramipril methyl ester),
[4]ethyl (2S)-2-[(3S,5aS,8aS,9aS)-3-methyl-1,4-dioxodecahydro-2H-cyclopenta[4,5]pyrrolo[1,2-a]pyrazin-2-yl]-4-phenylbutanoate(ramipril diketopiperazine),

Inject reference solution (c). The test is not valid unless the resolution between the peaks due to ramipril impurity K and ramipril impurity A is not less than 1.0.

For capsules containing more than 1.25 mg of Ramipril-

Inject reference solution (a), (b) and the test solution. Run the chromatogram 3 times the retention time of the principal peak, the sum of areas of the peaks corresponding to ramipril impurity D and ramipril impurity E is not more than 1.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (6.0 per cent), the area of any other secondary peak is not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent) and the sum of the areas of all the secondary peaks is not more than 1.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (6.0 per cent).

For capsules containing 1.25 mg or less of Ramipril-

Inject reference solution (a), (b) and the test solution. Run the chromatogram 3 times the retention time of the principal peak, the sum of the areas of the peaks corresponding to ramipril impurity D and ramipril impurity E is not more than 1.6 times the area of the principal peak in the chromatogram obtained with reference solution (a) (8.0 per cent), the area of any other secondary peak is not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent) and the sum of the areas of all the secondary peaks is not more than 1.6 times the area of the principal peak in the chromatogram obtained with reference solution (a) (8.0 per cent).

Ramipril Tablets. Page 3457

Insert before **Uniformity of content**
Related substances. Determine by liquid chromatography (2.4.14).

Test solution. Disperse a quantity of powdered tablets containing 25 mg of Ramipril in the mobile phase with the aid of ultrasound for 10 minutes and dilute to 50.0 ml with the mobile phase. Centrifuge and use the clear supernatant.

Reference solution (a). A0.0025 per cent w/v solution of *ramipril IPRS* in the mobile phase.

Reference solution (b). Dilute 5.0 ml of reference solution (a) to 25.0 ml with the mobile phase.

Reference solution (c). A solution containing 0.05 per cent w/v of *ramipril IPRS* and0.0005 per cent w/v, each of, *ramipril impurity A IPRS, ramipril impurity D IPRS* and *ramipril impurity K IPRS,* in the mobile phase.

Chromatographic system
- a stainless steel column 12.5 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (Such as Nucleosil 100-C18),
- mobile phase: a mixture of 68 volumes of a buffer solution containing 1.4 per cent w/v of *sodium perchlorate* and 0.58 per cent w/v of *orthophosphoric acid*, adjusted to pH 3.9 with *triethylamine* and 35 volumes of *acetonitrile,* adjust the pH 2.6 with *orthophosphoric acid*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 210 nm,
- injection volume: 15 µl.

Name	Relative retention time
Ramipril impurity E[1]	0.3
Ramipril impurity K[2]	0.5
Ramipril impurity A[3]	0.7
Ramipril(Retention time: about 10 minutes)	1.0
Ramipril impurity D[4]	2.6

[1](2S,3aS,6aS)-1-[(2S)-2-[[(1S)-1-carboxy-3-phenylpropyl]amino]propanoyl]octahydrocyclopenta[b]pyrrole-2-carboxylic acid (ramiprilat),
[2](2S)-2-[(3S,5aS,8aS,9aS)-3-methyl-1,4-dioxodecahydro-2H-cyclopenta[4,5]pyrrolo[1,2-a]pyrazin-2-yl]-4-phenylbutanoic acid (ramiprilate diketopiperazine),
[3](2S,3aS,6aS)-1-[(2S)-2-[[(2S)-1-methoxy-1-oxo-4-phenylbutan-2-yl]amino]propanoyl]octahydrocyclopenta[b]pyrrole-2-carboxylicacid (ramipril methyl ester),
[4]ethyl (2S)-2-[(3S,5aS,8aS,9aS)-3-methyl-1,4-dioxodecahydro-2H-cyclopenta[4,5]pyrrolo[1,2-a]pyrazin-2-yl]-4-phenylbutanoate(ramipril diketopiperazine),

Inject reference solution (c). The test is not valid unless the resolution between the peaks due to ramipril impurity K and ramipril impurity A is not less than 1.0.

For tablets containing more than 1.25 mg of Ramipril-

Inject reference solution (a), (b) and the test solution. Run the chromatogram 3 times the retention time of the principal peak, the sum of the areas of the peaks corresponding to ramipril impurity D and ramipril impurity E is not more than 1.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (6.0 per cent), the area of any other secondary peak is not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent) and the sum of the areas of all the secondary peaks is not more than 1.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (6.0 per cent).

For tablets containing 1.25 mg or less of Ramipril-

Inject reference solution (a), (b) and the test solution. Run the chromatogram 3 times the retention time of the principal peak, the sum of the areas of the peaks corresponding to ramipril impurity D and ramipril impurity E is not more than 1.6 times the area of the principal peak in the chromatogram obtained with reference solution (a) (8.0 per cent), the area of any other secondary peak is not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent) and the sum of the areas of all the secondary peaks is not more than 1.6 times the area of the principal peak in the chromatogram obtained with reference solution (a) (8.0 per cent).

Ropinirole Prolonged-release Tablets. Page 3522

Assay. *Test solution*, line 2 and 3
Change **from**: Ropinirole Hydrochloride
to: ropinirole

Reference solution (a)
Change **from**: A 0.011 per cent w/v solution of *ropinirole hydrochloride IPRS* in the solvent mixture.
to: A solution of *ropinirole hydrochloride IPRS* containing 0.01 per cent w/v of ropinirole in the solvent mixture.

Reference solution (b)
Change **from**: A solution containing 0.01 per cent w/v of *ropinirole hydrochloride IPRS* and 0.0003 per cent w/v of *ropinirole impurity B IPRS* in the solvent mixture.
to: A solution of *ropinirole hydrochloride IPRS* containing 0.01 per cent w/v ropinirole and 0.0003 per cent w/v of *ropinirole impurity B IPRS* in the solvent mixture.

Ropinirole Tablets. Page 3524

Related substances. *Test solution*, line 2
Change **from**: ropinirole hydrochloride
to: ropinirole

Reference solution (a)
Change **to**: *Reference solution (a)*. A solution of *ropinirole hydrochloride IPRS* in the solvent mixture containing 0.002 per cent w/v of *ropinirole*. Dilute 1.0 ml of the solution to 100.0 ml with the solvent mixture.

Rupatadine Fumarate. Page 3536

Related substances
Change **to**: **Related substances**. Determine by liquid chromatography (2.4.14).

Solvent mixture. 20 volumes of *acetonitrile* and 80 volumes of mobile phase A.

Test solution. Dissolve 32 mg of the substance under examination in the solvent mixture and dilute to 50.0 ml with the solvent mixture.

Reference solution (a). A 0.0064 per cent w/v solution of *rupatadine fumarate IPRS* in the solvent mixture. Dilute 1.0 ml of the solution to 100.0 ml with the solvent mixture.

Reference solution (b). Dissolve 3 mg of *rupatadine for system suitability IPRS (containing rupatadine impurity A and B)* in the solvent mixture and dilute to 5.0 ml with the solvent mixture.

Chromatographic system
- a stainless steel column 15 cm x 4.6 mm, packed with end-capped octadecylsilane bonded to porous silica (5 µm),
- column temperature: 30°,
- mobile phase: A. a 0.7 per cent w/v solution of *sodium dihydrogen orthophosphate* in *water,*
  B. *acetonitrile,*
- a gradient programme using the conditions given below,
- flow rate: 1.2 ml per minute,
- spectrophotometer set at 210 nm,
- injection volume: 50 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	80	20
2	80	20
27	50	50
28	80	20
35	80	20

Name	Relative retention time	Correction factor
Fumaric acid	0.1	---
Rupatadine impurity A[1]	0.6	1.3
Rupatadine impurity B[2]	0.7	---
Rupatadine (retention time: about 17 minutes)	1.0	---

[1]3-[[4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)piperidin-1-yl]methyl]-1-(1,2-dicarboxyethyl)-5-methylpyridin-1-ium
[2]8-chloro-11-(piperidin-4-ylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine,

Inject reference solution (b). The test is not valid unless the resolution between the peaks due to rupatadine impurity A and rupatadine impurity B is not less than 5.0.

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to rupatadine impurity A is not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a)(0.15 per cent),the area of any peak corresponding to rupatadine impurity B is not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a)(0.5 per cent),the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent)and the sum of the areas of all the secondary peaks is not more than 7 times the area of the principal peak in the chromatogram with reference solution (a) (0.7 per cent). Ignore the peak due to fumaric acid and any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Sulphated ash
Change **from**:0.2 per cent
to: 0.1 per cent

Loss on drying
Change **to**: **Loss on drying** (2.4.19). Not more than 0.5 per cent, determined on 1.0 g by drying in a vacuum oven at 80° for 3 hours.

Assay
Change **to**: **Assay**. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve 25 mg of the substance under examination in the mobile phase and dilute to 50.0 ml with the mobile phase. Dilute 5.0 ml of the solution to 50.0 ml with the mobile phase.

Reference solution. A 0.005 per centw/v solution of *rupatadine fumarate IPRS* in the mobile phase.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm),
- mobile phase: a mixture of 40 volumes of a buffer solution prepared by dissolving 6.8 g of *potassium dihydrogen orthophosphate* in 1000 ml with *water,* adjusted to pH 2.8 with *orthophosphoric acid*, 30 volumes of *acetonitrile* and 30 volumes of *methanol*,
- flow rate: 1 ml per minute,

– spectrophotometer set at 210 nm,
– injection volume: 20 µl.

Inject the reference solution. The test is not valid unless the relative standard deviation for replicate injections is not more than 2.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{30}F_{30}ClN_3O_4$.

Insert at the end
Storage. Store protected from light and moisture.

Salbutamol. Page 3548

Insert before **Related substances**
Optical rotation (2.4.22). –0.10° to +0.10°, determined in a 2.0 per cent w/v solution in *methanol*.

Impurity J (salbutamone). Not more than 0.2 per cent.
Dissolve 50.0 mg of the substance under examination in 0.1 per cent w/v of *hydrochloric acid* and dilute to 25.0 ml with the same solvent. The absorbance of the solution measured at 310 nm (2.4.7) is not more intense than 0.10.

Related substances
Change **to**: **Related substances**. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve 100 mg of the substance under examination in the mobile phase and dilute to 50.0 ml with the mobile phase.

*Reference solution (a).*A solution containing 0.02 per cent w/v, each of, *salbutamol IPRS* and *salbutamol impurity B IPRS* and 0.03 per cent w/v, each of, *salbutamol impurity D IPRS, salbutamol impurity F IPRS* and *salbutamol impurity G IPRS* in the mobile phase. Dilute 2.0 ml of the solution to 100.0 ml with the mobile phase.

Reference solution (b). A 0.0001 per cent w/v solution of *salbutamol IPRS* in the mobile phase.

Chromatographic system
– a stainless steel column 15 cm x 3.9 mm, packed with endcapped octylsilane bonded to porous silica with a specific surface area of 335 m^2/g, a pore size of 10 nm and a carbon loading of 11.7 per cent (5 µm),
– mobile phase: a mixture of 78 volumes of a buffer solution prepared by dissolving 2.87 g of *sodium heptanesulphonate* and 2.5 g of *potassium dihydrogen orthophosphate* in 1000 ml of *water*, adjusted to pH 3.65 with *orthophosphoric acid* and 22 volumes of *acetonitrile*,
– flow rate: 1 ml per minute,
– spectrophotometer set at 220 nm,
– injection volume: 20 µl.

Name	Relative retention time
Salbutamol (retention time about 2 minutes)	1.0
Salbutamol impurity B[1]	1.3
Salbutamol impurity A[2]	1.7
Salbutamol impurity C[3]	2.0
Salbutamol impurity D[4]	2.7
Salbutamol impurity H[5]	3.0
Salbutamol impurity E[6]	3.1
Salbutamol impurity G[7]	4.1
Salbutamol impurity F[8]	6.2
Salbutamol impurity I[9]	23.2

[1](1RS)-2-[(1,1-dimethylethyl)amino]-1-(4-hydroxyphenyl)ethanol,
[2]5-[(1RS)-2-[(1,1-dimethylethyl)amino]-1-methoxyethyl]-2-hydroxyphenyl]methanol,
[3](1RS)-2-[(1,1-dimethylethyl)amino]-1-(4-hydroxy-3-methylphenyl)ethanol,
[4]5-[(1RS)-2-[(1,1-dimethylethyl)amino]-1-hydroxyethyl]-2-hydroxybenzaldehyde,
[5]4-[2-[(1,1-dimethylethyl)amino]ethyl]-2-methylphenol,
[6](1RS)-2-[benzyl(1,1-dimethylethyl)amino]-1-[4-hydroxy-3-(hydroxymethyl)phenyl]ethanol,
[7]2-[benzyl(1,1-dimethylethyl)amino]-1-[4-hydroxy-3-(hydroxymethyl)phenyl]ethanone,
[8]1,1′-[oxybis[methylene(4-hydroxy-1,3-phenylene)]]bis[2-[(1,1-dimethylethyl)amino]ethanol],

[9](1RS)-2-[(1,1-dimethylethyl)amino]-1-[4-(benzyloxy)-3-(hydroxymethyl)phenyl]ethanol.

Inject reference solution (a) to identify the peaks due to salbutamol impurity B, D, F and G.

Inject reference solution (a). The test is not valid unless the resolution between the peaks due to salbutamol and salbutamol impurity B is not less than 3.0.

Inject reference solution (a), (b) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to salbutamol impurity D, F and G, each of, is not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.3 per cent),the area of any peak corresponding to salbutamol impurity A, B, C, E, H and I, each of, is not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent),the area of any other secondary peak is not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent)and the sum of the areas of all the secondary peaks is not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent).Ignore any peak with an area less than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Salbutamol Sulphate. Page 3550

Insert before **Related substances**

Optical rotation (2.4.22). –0.10° to +0.10°, determined in a 1.0 per cent w/v solution in *carbon dioxide-free water*.

Related substances

Change **to**: **Related substances**. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve 20 mg of the substance under examination in mobile phase A and dilute to 50.0 ml with mobile phase A.

Reference solution (a). A solution containing 0.00012 per cent w/v, each of, *salbutamol impurity D IPRS* and *salbutamol impurity F IPRS* in mobile phase A.

Reference solution (b). A 0.004 per cent w/v solution of *salbutamol IPRS* in mobile phase A. Dilute 1.0 ml of the solution to 100.0 ml with mobile phase A.

Reference solution (c). Dissolve the content of a vial of *salbutamol impurity J IPRS* in 1.0 ml of the test solution.

Reference solution (d). A 0.001 per cent w/v solution of *salbutamol impurity D IPRS* in mobile phase A.

Reference solution (e). Dilute 0.4 ml of reference solution (d) to 10.0 ml with mobile phase A. Dissolve the content of a vial of *salbutamol sulphate system suitability IPRS (containing impurity C, F, N and O)* in 1.0 ml of this solution.

Chromatographic system

- a stainless steel column 15 cm x 4.6 mm, packed with endcapped octylsilane bonded to porous silica (3 µm),
- mobile phase: A. a buffer solution prepared by dissolving 3.45 g of *sodium dihydrogen orthophosphate monohydrate* in 900 ml of 0.05 per cent v/v solution of *triethylamine*, adjusted to pH 3.0 with *orthophosphoric acid* and dilute to 1000 ml with 0.05 per cent v/v solution of *triethylamine*,
  B. a mixture of 35 volumes of *methanol* and 65 volumes of *acetonitrile*,
- a gradient programme using the conditions given below,
- flow rate: 1 ml per minute,
- spectrophotometer set at 273 nm,
- injection volume: 20 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	95	5
5	95	5
30	10	90
35	95	5

Name	Relative retention time
Salbutamol impurity J[1]	0.9
Salbutamol (Retention time: about 7 minutes)	1.0
Salbutamol impurity C[2]	1.6
Salbutamol impurity N[3]	1.67

Salbutamol impurity D[4]	1.68
Salbutamol impurity F[5]	1.77
Salbutamol impurity O[6]	1.82

[1]2-[(1,1-dimethylethyl)amino]-1-[4-hydroxy-3-(hydroxymethyl)phenyl]ethanone (salbutamone),
[2](1RS)-2-[(1,1-dimethylethyl)amino]-1-(4-hydroxy-3-methylphenyl)ethanol,
[3]2-[(1,1-dimethylethyl)amino]-1-[3-[[5-[2-[(1,1-dimethylethyl)amino]-1-hydroxyethyl]-2-hydroxyphenyl]methyl]-4-hydroxy-5-(hydroxymethyl)phenyl]ethanol,
[4]5-[(1RS)-2-[(1,1-dimethylethyl)amino]-1-hydroxyethyl]-2-hydroxybenzaldehyde,
[5]1,1′-[oxybis[methylene(4-hydroxy-1,3-phenylene)]]bis[2-[(1,1-dimethylethyl)amino]ethanol],
[6]unknown structure.

Inject reference solution (c) and (e). The test is not valid unless the peak-to-valley ratio is not less than 1.2, where *Hp* is the height above the baseline of the peak due to salbutamol impurity N and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to salbutamol impurity D in the chromatogram obtained with reference solution (e) and not less than 2.0, where *Hp* is the height above the baseline of the peak due to salbutamol impurity J and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to salbutamol in the chromatogram obtained with reference solution (c).

Inject reference solution (e) to identify the peaks due to salbutamol impurity C, D, F, N and O. Inject reference solution (c) to identify the peak due to salbutamol impurity J.

Inject reference solution (a), (b) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to salbutamol impurity D and F, each of, is not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.3 per cent),the area of any peak corresponding to salbutamol impurity C, N and O, each of, is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent),the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent)and the sum of the areas all the secondary peaks is not more than 9 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.9 per cent).Ignore any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Salbutamol Injection. Page 3552

Insert before **Related substances**

Salbutamol ketone. Determine by liquid chromatography (2.4.14).

Test solution. Dilute a volume of injection, if necessary, with *water* to obtain a solution containing 0.025 per cent w/v of salbutamol.

Reference solution. A 0.00025 per cent w/v solution of *salbutamol ketone impurity IPRS (salbutamol impurity J))* in *water*.

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with endcapped octylsilane bonded to porous silica (5 µm) (Such as Hypersil BDS C8),
- mobile phase: A. a mixture of 98.5 volumes of *0.1 M ammonium acetate* and 1.5 volume of *2-propanol*, adjusted to pH 4.5 with *glacial acetic acid,*
  B. *2-propanol,*
- a gradient programme using the conditions given below,
- flow rate: 1 ml per minute,
- spectrophotometer set at 276 nm,
- injection volume: 20 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	100	0
5	100	0
20	86	14
30	86	14
31	100	0
45	100	0

Inject the reference solution and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to salbutamol Ketone (salbutamol impurity J) is not more 0.5 times than the area of the principal peak in the chromatogram obtained with the reference solution (0.5 per cent).

Related substances

Change **to: Related substances**. Determine by liquid chromatography (2.4.14).

Test solution. Dilute a volume of injection with the mobile phase to obtain a solution containing 0.005 per cent w/v of salbutamol.

Reference solution (a). A solution of *salbutamol sulphate IPRS* containing 0.00005 per cent w/v of salbutamol in the mobile phase.

Reference solution (b). A solution containing 0.0004 per cent w/v of *salbutamol impurity B IPRS* and 0.0005 per cent w/v of *salbutamol sulphate IPRS* in the mobile phase.

Reference solution (c). A 0.000025 per cent w/v solution of *salbutamol impurity D IPRS* in the mobile phase.

Reference solution (d). Dilute 1.0 ml of reference solution (a) to 10.0 ml with the mobile phase.

Chromatographic system
- a stainless steel column 15 cm x 3.9 mm, packed with endcapped octylsilane bonded to porous silica (5 µm) with a specific surface area of 335 m^2 per g, a pore size of 10 nm and a carbon loading of 11.7 per cent (Such as Symmetry C8),
- mobile phase: a mixture of 22 volumes of *acetonitrile* and 78 volumes of a solution containing 0.29 per cent w/v of *sodium heptane sulphonate* and 0.25 per cent w/v of *potassium dihydrogen orthophosphate,* adjusted to pH 3.65 with *2Morthophosphoric acid,*
- flow rate: 1 ml per minute,
- spectrophotometer set at 220 nm,
- injection volume: 20 µl.

The relative retention time with reference to salbutamol (retention time: about 2 minutes) for salbutamol impurity D is about 2.7.

Inject reference solution (b). The test is not valid unless the resolution between the two principal peaks is not less than 3.0.

Inject reference solution (a), (c), (d) and the test solution. Run the chromatogram 25 times the retention time of the principal peak. In the chromatogram obtained with the test solution, the area of any peak corresponding to salbutamol impurity D is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (c) (1.0 per cent), the area of any other secondary peak is not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent) and the sum of the areas of all the secondary peaks is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (2.0 per cent). Ignore any peak with an area less than the area of the principal peak in the chromatogram obtained with reference solution (d) (0.1 per cent).

Assay.
Change **to**: **Assay**. Determine by liquid chromatography (2.4.14).

Test solution. Dilute a volume of injection with sufficient quantity of *water* to obtain a solution containing 0.0025 per cent w/v of salbutamol.

Reference solution (a). A 0.003 per cent w/v solution of *salbutamol sulphate IPRS* in the mobile phase.

Reference solution (b). A solution containing 0.003 per cent w/v of *salbutamol sulphate IPRS* and 0.0025 per cent w/v of *salbutamol impurity C IPRS (2-tert-butylamine-1(4-hydroxy-3-methylphenyl) ethanol))* in the mobile phase.

Chromatographic system
- a stainless steel column 20 cm x 5 mm, packed with cyanosilyl bonded to porous silica (5 µm) (Such as Spherisorb CN),
- mobile phase: a mixture of 30 volumes of *0.05M ammonium acetate,* 68.5 volumes of *water* and 1.5 volumes of *2-propanol*, adjusted to pH 4.5 with *glacial acetic acid,*
- flow rate: 2 ml per minute,
- spectrophotometer set at 276 nm,
- injection volume: 20 µl.

Inject reference solution (b). The test is not valid unless the resolution between the two principal peaks is not less than 3.0.

Inject reference solution (a) and the test solution.

Calculate the content of $C_{13}H_{21}NO_3$ in the Injection.1 mg of $(C_{13}H_{21}NO_3S)_2$. H_2SO_4 is equivalent to 0.83 mg of $C_{13}H_{21}NO_3$.

Sertraline Tablets. Page 3576

Enantiomeric purity. Delete the requirement.

Related substances. After chromatographic system, para 2, lines 2 to 7

Change **from**: the area of any peak corresponding to sertraline impurity C (1RS,4RS)-4-(4-chlorophenyl)-N-methyl-1,2,3,4-tetrahydronaphthalen-1-amine) is not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.8 per cent).

to: the sum of areas of any peaks corresponding to sertraline impurity C (1*RS*,4*RS*)-4-(4-chlorophenyl)-*N*-methyl-1,2,3,4-tetrahydronaphthalen-1-amine) and sertraline impurity D (1*RS*,4*RS*)-4-(3-chlorophenyl)-*N*-methyl-1,2,3,4-tetrahydronaphthalen-1-amine) is not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.8 per cent).

Simvastatin. Page 3583

Related substances. Para 1

Change **to**:

Name	Relative retention time
Simvastatin impurity A[1]	0.45
Simvastatin impurity E[2*] and F[3*]	0.60
Simvastatin impurity G[4]	0.80
Simvastatin	1.0
Simvastatin impurity B[5]	2.38
Simvastatin impurity C[6]	2.42
Simvastatin impurity D[7]	3.80

*If present, simvastatin impurity E (lovastatin) and simvastatin impurity F (epilovastatin) may not be completely resolved by the method. These peaks are integrated together to determine conformance,

[1](3*R*,5*R*)-7-[(1*S*,2*S*,6*R*,8*S*,8a*R*)-8-[(2,2-dimethylbutanoyl)oxy]-2,6-dimethyl-1,2,6,7,8,8a-hexahydronaphthalen-1-yl]-3,5-dihydroxyheptanoic acid,

[2]lovastatin,

[3](1*S*,3*R*,7*S*,8*S*,8a*R*)-8-[2-[(2*R*,4*R*)-4-hydroxy-6-oxotetrahydro-2*H*-pyran-2-yl]ethyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl (2*R*)-2-methylbutanoate (epilovastatin),

[4](1*S*,7*S*,8*S*,8a*R*)-8-[2-[(2*R*,4*R*)-4-hydroxy-6-oxotetrahydro-2*H*-pyran-2-yl]ethyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl 2,2-dimethylbut-3-enoate,

[5](1*S*,3*R*,7*S*,8*S*,8a*R*)-8-[2-[(2*R*,4*R*)-4-(acetyloxy)-6-oxotetrahydro-2*H*-pyran-2-yl]ethyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl 2,2-dimethylbutanoate (acetate ester),

[6](1*S*,3*R*,7*S*,8*S*,8a*R*)-3,7-dimethyl-8-[2-[(2*R*)-6-oxo-3,6-dihydro-2*H*-pyran-2-yl]ethyl]-1,2,3,7,8,8a-hexahydronaphthalen-1-yl 2,2-dimethylbutanoate (anhydro-simvastatin),

[7](2*R*,4*R*)-2-[2-[(1*S*,2*S*,6*R*,8*S*,8a*R*)-8-[(2,2-dimethylbutanoyl) oxy]-2,6-dimethyl-1,2,6,7,8,8a-hexahydronaphthalen-1-yl]ethyl]-6-oxotetrahydro-2*H*-pyran-4-yl (3*R*, 5*R*)-7-[(1*S*,2*S*,6*R*, 8*S*,8a*R*)-8-[(2,2-dimethylbutanoyl) oxy]-2,6-dimethyl-1,2,6,7,8, 8a-hexahydronaphthalen1-yl]-3,5-dihydroxyheptanoate.

Assay. After chromatographic system, para 1

Change **to**: Inject reference solution (a) and (c). The test is not valid unless the resolution between the peaks due to lovastatin and simvastatin is not less than 3.0 in the chromatogram obtained with reference solution (a) and the relative standard deviation for replicate injections is not more than 1.0 per cent in the chromatogram obtained with reference solution (c).

Simvastatin Tablets. Page 3584

Related substances

Change **to**: **Related substances**. Determine by liquid chromatography (2.4.14).

Solvent mixture. 40 volumes of a 0.14 per cent w/v solution of *potassium dihydrogen phosphate* in *water*, adjusted to pH 7.0 with *dilute ammonia solution* and 60 volumes of *acetonitrile*.

Test solution. Disperse a quantity of the powdered tablets containing 75 mg of the Simvastatin in the solvent mixture with the aid of ultrasound with intermittent shaking for 5 minutes and dilute to 50.0 ml with the solvent mixture, filter.

Reference solution (a). A solution containing 0.00075 per cent w/v of *simvastatin IPRS* and *tenivastatin calcium IPRS* equivalent to 0.0015 per cent w/v of *tenivastatin*in the solvent mixture.

Reference solution (b). A solution containing 0.002 per cent w/v, each of, *simvastatin IPRS* and *lovastatin IPRS* in the solvent mixture.

Chromatographic system

- a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (Such as Zorbax Eclipse XDB-C18),

– sample temperature: 10º,
– mobile phase: A. a mixture of 45 volumes of *acetonitrile* and 55 volumes of a 0.1 per cent v/v solution of *orthophosphoric acid* in *water*,
B. a mixture of 90 volumes of *acetonitrile* and 10 volumes of a 0.1 per cent v/v solution of *orthophosphoric acid* in *water*,
– a gradient programme using the conditions given below,
– flow rate: 2 ml per minute,
– spectrophotometer set at 238 nm,
– injection volume: 20 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	100	0
38	100	0
40	65	35
50	65	35
70	0	100
90	0	100
92	100	0
100	100	0

Name	Relative retention time
Simvastatin impurity A[1]	0.43
Simvastatin impurity E[2*]	0.63
Simvastatin impurity F[3*]	0.66
Simvastatin impurity G[4*]	0.80
Simvastatin	1.0
Tenivastatin methyl ester[5*]	1.14
Simvastatin impurity B[6*]	1.54
Simvastatin impurity C[7*]	1.59
Simvastatin impurity D[8*]	2.30

*Process impurity included in the table for identification purposes only. Process impurities are controlled in the drug substance, and are not to be reported or included in the total impurities for the drug product,
[1](3*R*,5*R*)-7-[(1*S*,2*S*,6*R*,8*S*,8a*R*)-8-[(2,2-dimethylbutanoyl)oxy]-2,6-dimethyl-1,2,6,7,8,8a-hexahydronaphthalen-1-yl]-3,5-dihydroxyheptanoic acid (tenivastatin),
[2]lovastatin,
[3](1*S*,3*R*,7*S*,8*S*,8a*R*)-8-[2-[(2*R*,4*R*)-4-hydroxy-6-oxotetrahydro-2*H*-pyran-2-yl]ethyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl (2*R*)-2-methylbutanoate (epilovastatin),
[4](1*S*,7*S*,8*S*,8a*R*)-8-[2-[(2*R*,4*R*)-4-hydroxy-6-oxotetrahydro-2*H*-pyran-2-yl]ethyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl 2,2-dimethylbut-3-enoate,
[5]Methyl (3*R*,5*R*)-7-{(1*S*,2*S*,6*R*,8*S*,8a*R*)-8-[(2,2-dimethylbutanoyl)oxy]-2,6-dimethyl-1,2,6,7,8,8a-hexahydronaphthalen-1-yl}-3,5-dihydroxyheptanoate.
[6](1*S*,3*R*,7*S*,8*S*,8a*R*)-8-[2-[(2*R*,4*R*)-4-(acetyloxy)-6-oxotetrahydro-2*H*-pyran-2-yl]ethyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl 2,2-dimethylbutanoate (acetate ester),
[7](1*S*,3*R*,7*S*,8*S*,8a*R*)-3,7-dimethyl-8-[2-[(2*R*)-6-oxo-3,6-dihydro-2*H*-pyran-2-yl]ethyl]-1,2,3,7,8,8a-hexahydronaphthalen-1-yl 2,2-dimethylbutanoate (anhydro-simvastatin),
[8](2*R*,4*R*)-2-[2-[(1*S*,2*S*,6*R*,8*S*,8a*R*)-8-[(2,2-dimethylbutanoyl) oxy]-2,6-dimethyl-1,2,6,7,8,8a-hexahydronaphthalen-1-yl]ethyl]-6-oxotetrahydro-2*H*-pyran-4-yl (3*R*, 5*R*)-7-[(1*S*,2*S*,6*R*, 8*S*,8a*R*)-8-[(2,2-dimethylbutanoyl) oxy]-2,6-dimethyl-1,2,6,7,8, 8a-hexahydronaphthalen1-yl]-3,5-dihydroxyheptanoate.

Inject reference solution (a) and (b). The test is not valid unless the resolution between the peaks due to simvastatin and lovastatin is not less than 8.0 in the chromatogram obtained with reference solution (b) and the tailing factor is not more than 1.5 for simvastatin peak in the chromatogram obtained with reference solution (a).

Inject reference solution (a) and the test solution. Run the chromatogram 3 times the retention time of the principal peak. The area of any peak corresponding to simvastatin impurity A is not more than the area the tenivastatin peak in the chromatogram obtained with reference solution (a) (1.0 per cent), the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent) and the sum of the areas of all the secondary peaks other than lovastatin is not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (2.0 per cent).

Assay. After chromatographic system, para 1
Insert at the end
and the relative standard deviation for replicate injections is not more than 2.0 per cent.

Sitagliptin Tablets. Page 5278

Dissolution. After chromatographic system, para 1, line 2
Change **from**: not more than
to: not less than

Sulphamethoxazole. Page 3687

Para 2
Sulphamethoxazole contains not less than 98.0 per cent and not more than 102.0 per cent of $C_{10}H_{11}N_3O_3S$, calculated on the dried basis.

Identification. B
Change **to**: B. In the Assay, the principal peak in the chromatogram obtained with test solution (b) corresponds to peak in the chromatogram obtained with reference solution (e).

Related substances. Change **to**:
Related substances. Determine by liquid chromatography (2.4.14).

Test solution (a). Dissolve 0.1 g of the substance under examination in the mobile phase with the aid of ultrasound at 45° with intermittent shaking and dilute to 100.0 ml with the mobile phase.

Test solution (b). Dilute 1.0 ml test solution (a) to 10.0 ml with the mobile phase.

Reference solution (a). A solution containing 0.0001 per cent w/v, each of, *sulphamethoxazole IPRS* and *sulphamethoxazole related compound F IPRS* in the mobile phase.

Reference solution (b). A solution containing 0.0001 per cent w/v, each of, *sulphamethoxazole related compound A IPRS, sulphamethoxazole related compound B IPRS, sulphamethoxazole related compound C IPRS, sulphanilic acid IPRS* and *sulphanilamide IPRS* in the mobile phase.

Reference solution (c). A 0.003 per cent w/v solution of *sulphamethoxazole IPRS* in the mobile phase. Dilute 1.0 ml of the solution to 100.0 ml with the mobile phase.

Reference solution (d). A solution containing 0.01 per cent w/v, each of, *sulphamethoxazole IPRS* and *sulphamethoxazole related compound A IPRS* in the mobile phase. Sonicate at 45° with intermittent shaking to dissolve before final dilution.

Reference solution (e). A 0.01 per cent w/v solution of *sulphamethoxazole IPRS* in the mobile phase. Sonicate at 45° with intermittent shaking to dissolve before final dilution.

Chromatographic system
- a stainless steel column 25 cm x 4.0 mm, packed with octylsilane bonded to porous silica (5 µm),
- mobile phase: a mixture of 70 volumes of a buffer solution prepared by dissolve 13.6 g of *potassium dihydrogen phosphate* in 1000 ml of *water,* adjusted to pH 5.3 with 2 per cent w/v solution of *potassium hydroxide* and 30 volumes of *methanol,*
-flow rate: 0.9 ml per minute,
- spectrophotometer set at 210 nm,
- injection volume: 20 µl.

Name	Relative retention time
Sulphanilic acid[1]	0.26
Sulphanilamide[2]	0.35
Sulphamethoxazole related compound F[3]	0.45
Sulphamethoxazole related compound C[4]	0.50
Sulphamethoxazole	1.00
Sulphamethoxazole related compound A[5]	1.20
Sulphamethoxazole related compound B[6]	2.10

[1]4-Aminobenzenesulfonic acid.
[2]4-Aminobenzenesulfonamide.
[3]4-Amino-N-(3-methylisoxazol-5-yl)benzenesulfonamide.
[4]5-Methylisoxazol-3-amine.
[5]N-{4-[N-(5-Methylisoxazol-3-yl)sulfamoyl]phenyl}acetamide.
[6]4-Amino-N-{4-[N-(5-methylisoxazol-3-yl)sulfamoyl]phenyl}benzenesulfonamide.

Inject reference solution (b) to identify the peaks due to sulphamethoxazole related compound A, B, C, sulphanilic acid and sulphanilamide.

Inject reference solution (a), (c) and (d). The test is not valid unless the resolution between the peaks due to sulphamethoxazole and sulphamethoxazole related compound A is not less than 3.5 in the chromatogram obtained with reference solution (d), the relative standard deviation for replicate injections is not more than 5.0 per cent for both the peaks in the chromatogram obtained with reference solution (a) and the signal-to-noise ratio for the principal peak is not less than 10.0 in the chromatogram obtained with reference solution (c).

Inject reference solution (a) and test solution (a). In the chromatogram obtained with test solution (a), the area of any peak corresponding to sulphamethoxazole related compound F is not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.1 per cent), the area of any secondary peak corresponding to sulphanilic acid, sulphanilamide, sulphamethoxazole related compound A, B and C, each of, is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent), the area of any secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent) and the sum of the areas of all the secondary peaks is not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent). Ignore any peak with an area less than 0.3 times the area of the principal peak in the chromatogram obtained with the reference solution (a) (0.03 per cent).

Assay. Change **to**:
Assay. Determine by liquid chromatography (2.4.14), as described under Related substances with the following modifications.

The relative retention time with reference to sulphamethoxzole, for sulphamethoxazolerelated compound A is about 1.2.

Inject reference solution (d) and (e). The test is not valid unless the resolution between the peaks due to sulphamethoxazole and sulphamethoxazolerelated compound A is not less than 3.5 in the chromatogram obtained with reference solution (d) and the relative standard deviation for replicate injections is not more than 1.0 per cent in the chromatogram obtained with reference solution (e).

Inject reference solution (e) and test solution (b).

Calculate the content of $C_{10}H_{11}N_3O_3S$.

Telmisartan Tablets. Page 5287

Related substances. *Test solution*

Change **to**: *Test solution*. Transfer a suitable quantity of intact tablets (not less than 20 tablets) to a suitable volumetric flask, add about 80 per cent of the volume of the solvent mixture. Swirl to disperse and sonicate for 10 minutes, allow to cool to room temperature and dilute to volume with the solvent mixture and filter. Dilute a suitable volume of the filtrate with the mobile phase to obtain a solution having concentration 0.011 per cent w/v of Telmisartan.

Tamsulosin Hydrochloride. Page 3713

Related substances
Change **to**: **Related substances**. Determine by liquid chromatography(2.4.14).

Solvent mixture. 70 volumes of mobile phase A and 30 volumes of mobile phase B.

Test solution. Dissolve 0.1 g of the substance under examination in the solvent mixture, with the aid of ultrasound and dilute to 100.0 ml with the solvent mixture.

Reference solution (a). A 0.0001 per cent w/v solution of *tamsulosin hydrochloride IPRS* in the solvent mixture.

Reference solution (b). A solution containing 0.0001 per cent w/v, each of, *tamsulosin impurity AIPRS* and *tamsulosin impurity B IPRS* in reference solution (a).

Chromatographic system

- a stainlesssteel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica(5µm) (Such as Inert-sustain AQ C18),
- column temperature: 50º,

- mobile phase: A. a buffer solution prepared by dissolving 1.36 g of *potassium dihydrogen phosphate* in 1000 ml of *water*, adjusted to pH 2.0 with *orthophosphoric acid*,
  B. a mixture of 50 volumes of *acetonitrile* and 50 volumes of *methanol*,
- a gradient programme using the conditions given below,
- flow rate: 1 ml per minute,
- spectrophotometer set at 225 nm,
- injection volume:10µl.

Time (in min)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	72	28
5	72	28
20	65	35
48	30	70
57	25	75
57.1	72	28
65	72	28

Name	Relative retention time
Tamsulosin impurity A[1]	0.7
Tamsulosin (Retention time; about 17 minutes)	1.0
Tamsulosin impurity B[2]	1.96

[1]2-methoxy-5-[(2R)-2-{(2-(2-methoxyphenoxyethyl)amino)propyl)benzene sulphonamide,
[2](2R)-N-[2-(2-ethoxyphenoxy)ethyl]-1-(4-methoxyphenyl)propan-2-amine.

Inject reference solution (b). The test is not valid unless the resolution between the peaks due to tamsulosin impurity A and tamsulosin is not less than 6.0.

Inject reference solution (a), (b) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to tamsulosin impurity A and tamsulosin impurity B, each of, is not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.10 per cent),the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent) and the sum of the areas of all the secondary peaks is not more than twice the area of the principal peak in the chromatogram obtained with reference solution(a)(0.20 per cent). Ignore any peak with an area less than 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.03 per cent).

Tapentadol Hydrochloride. Page 3718

Identification. B

Change **to**: B. In the Assay, the principal peak in the chromatogram obtained with test solution (b) corresponds to the peak in the chromatogram obtained with reference solution (a).

Specific optical rotation

Change **to**: **Enantiomeric purity**. Determine by liquid chromatography (2.4.14).

Solvent mixture. 89.8 volumes of *heptane,*10 volumes of *2-propanol* and 0.2 volume of *diethylamine*.

Test solution. Dissolve 25 mg of the substance under examination in a mixture of 0.1 ml of *diethylamine* and 5 ml of *2-propanol* with the aid of ultrasound and dilute to50.0 ml with *heptane.*

Reference solution (a). A 0.005 per cent w/v solution of *tapentadol hydrochloride IPRS* in the solvent mixture. Dilute 1.0 ml of the solution to 100.0 ml with the solvent mixture.

Reference solution (b). Dissolve 5 mg, each of, *tapentadol impurity AIPRS* and *tapentadol hydrochloride IPRS* in a mixture of 0.2 ml of *diethylamine*and 10 ml of *2-propanol* with the aid of ultrasound and dilute to100.0 ml with *heptane.*

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with amylose derivative of silica gel for chiral separation (5 µm),
- mobile phase: a mixture of 98 volumes of *heptane,* 2 volumes of *2-propanol* and 0.1 volume of *diethylamine*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 270 nm,
- injection volume: 20 µl.

Name	Relative retention time
Tapentadol (Retention time: about 15 minutes)	1.0
Tapentadol impurity A[1]	1.2

[1]3-[(2*S*,3*S*)-1-(dimethylamino)-2-methylpentan-3-yl]phenol,

Inject reference solution (b). The test is not valid unless the resolution between the peaks due to tapentadol and tapentadol impurity A is not less than 2.0.

Inject reference solution (a) and the test solution. Run the chromatogram 1.5 times the retention time of the principal peak. In the chromatogram obtained with the test solution, the area of the any peak corresponding to tapentadol impurity A is not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent). Ignore any peak with an area less than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent).

Related substances. Change **to:**

Related substances. Determine by liquid chromatography (2.4.14).

Solvent mixture. 80 volumes of *water,* 20 volumes of *methanol* and 0.1 volume of *orthophosphoric acid.*

Test solution (a). Dissolve 30 mg of the substance under examination in the solvent mixture and dilute to 50.0 ml with the solvent mixture.

Test solution (b). Dilute 5.0 ml of test solution (a) to 50.0 ml with the solvent mixture.

Reference solution (a). A 0.006 per cent w/v solution of *tapentadol hydrochloride IPRS* in the solvent mixture.

Reference solution (b). Dilute 1.0 ml of reference solution (a) to 100.0 ml with the solvent mixture.

Reference solution (c). A solution containing 0.06 per cent w/v of *tapentadol hydrochloride IPRS* and 0.0006 per cent w/v of *tapentadol impurity CIPRS* in the solvent mixture.

Chromatographic system
- a stainless steel column 15 cm x 4.6 mm, packed with end-capped octadecylsilane bonded to porous silica (5 µm),
- mobile phase: A. a mixture of 90 volumes of *water,* 10 volumes of *methanol* and 0.1 volume of *orthophosphoric acid*,
  B. a mixture of 90 volumes of *methanol,* 10 volumes of *water* and 0.1 volume of *orthophosphoric acid*,
- a gradient programme using the conditions given below,
- flow rate: 1.5 ml per minute,
- spectrophotometer set at 215 nm,
- injection volume: 20 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	100	0
2	100	0
44	61	39
44.5	0	100
46	100	0
50	100	0

Name	Relative retention time
Tapentadol impurity C[1]	0.9
Tapentadol (Retention time: about 15 minutes)	1.0

[1]3-[(2*Z*, 4*R*)-5-(dimethylamino)-4-methylpent-2-en-3-yl]phenol.

Inject reference solution (c). The test is not valid unless the resolution between the peaks due to tapentadol impurity C and tapentadol is not less than 1.5.

Inject reference solution (b) and test solution (a). In the chromatogram obtained with test solution (a), the area of any secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent) and the sum of the areas of all the secondary peaks is not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.4 per cent).Ignore any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Assay. Change **to:**
Assay. Determine by liquid chromatography (2.4.14), as described under Related substances

Inject reference solution (a) and test solution (b).

Calculate the content of $C_{14}H_{24}ClNO$.

Tenofovir Disoproxil Fumarate. Page 3745

Insert before **Related substances**
S-isomer. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve 25 mg of the substance under examination in the mobile phase, with the aid of ultrasound and dilute to 25.0 ml with the mobile phase.

Reference solution. A solution containing 0.05 per cent w/v, each of, *tenofovir disoproxil fumarate IPRS* and *tenofovir s-isomer IPRS* in the mobile phase.

Chromatographic system
- a stainless steel column 25 cm x 4.6mm, packed with amylase tris-(3,5-dimethylphenyl carbamate) bonded to porous silica (5µm) (Such as Chiralpak AD-H),
- column temperature:40°,
- mobile phase: a mixture of 80 volumes of *ethanol,* 20 volumes of *n-hexane* and 0.05 volume of *triethylamine,*
- flow rate: 1 ml per minute,
- spectrophotometer set at 260 nm,
- injection volume: 20 µl.

The relative retention time with reference to tenofovir disoproxil, for s-isomer is about 1.86.

Inject the reference solution. The test is not valid unless the resolution between the peaks due to tenofovir disoproxil and tenofovir s-isomer is not less than 5.0, the column efficiency is not less than 3000 theoretical plates and the tailing factor is not more than 2.0, for tenofovir disoproxil peak.

Inject the reference solution and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to tenofovir s-isomer is not more than 0.02 times the area of the corresponding peak in the chromatogram obtained with the reference solution (1.0 per cent).

Related substances
Change **to**: **Related substances**
A. Determine by liquid chromatography (2.4.14).

Solvent mixture. Equal volumes of *water* and *methanol.*

Buffer solution. Dissolve 1.41 g of *disodium hydrogen orthophosphate* in 1000 ml of *water*, adjusted to pH 5.5 with *orthophosphoric acid.*

Test solution. Dissolve 50 mg of the substance under examination in the solvent mixture and dilute to 50.0 ml with the solvent mixture.

*Reference solution (a).*A 0.001 per cent w/v solution of *tenofovir disoproxil fumarate IPRS* in the solvent mixture.

*Reference solution (b).*A 0.005 per cent w/v solution of *tenofovir n-propyl impurity IPRS* in the solvent mixture. Transfer 1.5 ml of the solution to a 50-ml volumetric flask, and add 50 mg of *tenofovir disoproxil fumarate IPRS* and 30 ml of the solvent mixture, shake to dissolve and dilute to volume with the solvent mixture.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (Such as YMC pack ODS AQ),
- column temperature: 35°,
- sample temperature:5°,
- mobile phase: A. a mixture of 70 volumes of the buffer solution, 27.5 volumes of *methanol* and 2.5 volumes of *tertiary butanol*,

  B. a mixture of 30 volumes of the buffer solution, 67.5 volumes of *methanol* and 2.5 volumes of *tertiary butanol*,

— a gradient programme using the conditions given below,
— flow rate: 1 ml per minute,
— spectrophotometer set at 260 nm,
— injection volume: 20 µl.
NOTE – the method is found to be sensitive towards organic phase ratio in the mobile phase and it will have significant impact on theoretical plates of tenofovir disoproxil peak.

Time (in min)	Mobile phase A (per cent)	Mobile phase B (per cent)
0	100	0
2	100	0
30	0	100
45	0	100
50	100	0
60	100	0

Name	Relative retention time	Correction factor
Fumaric acid	0.11	---
Tenofovir impurity[1]	0.13	0.46
Adenine impurity[2]	0.15	0.23
Monoester impurity [3]	0.27	0.76
Ethyl impurity[4*]	0.68	0.72
Isopropyl impurity[5]	0.84	0.77
Tenofovir disoproxil	1.0	---
n-propyl impurity[6]	1.04	1.05
Carbonyl impurity[7]	1.36	0.93
Tenofovir disoproxil dimer impurity[8]	1.7	---

*Ethyl impurity peak may elute as split peak, consider it as a single peak.
[1](R)-1-(6-Amino-9H-purin-9-yl) propan-2-yloxy) methylphosphonic acid,
[2]9H-purin-6-amine,
[3] (1-methylethyl) (8R)-9-(6-amino-9H-purin-9-yl)-5-hydroxy-8-methyl-5-oxo-2,4,7-trioxa-5λ^5-phosphanonanoate,
[4]fumarate salt of isopropyloxycarbonyloxy methyl (ethoxy)-(R)-9-[2-phosphonomethoxy)propyl adenine,
[5](1-methylethyl)(5RS,8R)-9-(6-amino-9H-purin-9-yl)-8-methyl-5-(1-methylethyl)-5-oxo-2,4,7-trioxa-5λ^5-phosphanonanoate,
[6]1-methylethyl propyl (5RS)-5-{[(1R)-2-(6-amino-9H-yl)-1-methylethoxy]methyl}-5-oxo-2,4,7-trioxa-5λ^5-phosphanonanoate,
[7]O,O-Bis(isopropoxycarbonyloxymethyl){(R)-[1-[(6-isopropoxy-carbonylamino)-9H-purin-9-yl]propan-2-yloxy]}methyl phosphonate,
[8]Tetrakis (1-methylethyl)5,5'-(methylenebis{imino-9H-purine-6,9-diyl[(2R)-propane-1,2-dily]oxomethylene})bis-5-oxo-2,4,7-trioxa-5λ^5-phosphanonanoate,

Inject reference solution (a) and (b). The test is not valid unless the resolution between the peaks due to tenofovir disoproxil and tenofovirn-propyl impurity is not less than 1.5 in the chromatogram obtained with reference solution (b), the column efficiency is not less than 15000 theoretical plates, the tailing factor is not more than 2.0and the relative standard deviation for replicate injections is not more than 5.0 per cent in the chromatogram obtained with reference solution (a).

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to monoester impurity is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent),the area of any peak corresponding to isopropyl impurity is not more than 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent), the area of any peak corresponding to tenofovir impurity, adenine impurity, ethyl impurity, carbonyl impurity and n-propyl impurity, each of, is not more than 0.15 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent),the area of any other secondary peak is not more than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent)and the sum of the areas of all the secondary peaks is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (2.0 per cent). Ignore any peak due to fumaric acid and tenofovir disoproxil dimer impurity.

B. Determine by liquid chromatography (2.4.14).

Solvent mixture. Equal volume of *water* and *methanol.*

Test solution. Dissolve 50 mg of the substance under examination in the solvent mixture and dilute to 10.0 ml with the solvent mixture.

Reference solution. A 0.00075 per cent w/v solution of *tenofovir disoproxil fumarate IPRS* in the solvent mixture.

Chromatographic system

— a stainless steel column 10 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (3.5 µm) (Such as Zorbax Rx C18),
— column temperature:40°,
— sample temperature: 5°,
— mobile phase: A. a buffer solution prepared by dissolving 1.36 g of *potassium dihydrogen orthophosphate* in 1000 ml of *water*, adjusted to pH 5.5 with 10 per cent v/v solution of *potassium hydroxide,*
B. *acetonitrile*,
— a gradient programme using the conditions given below,
— flow rate: 1.5 ml per minute,
— spectrophotometer set at 260 nm,
— injection volume: 20 µl.

Time (in min)	Mobile phase A (per cent)	Mobile phase B (per cent)
0	80	20
25	30	70
25.1	80	20
28	80	20

Name	Relative retention time	Correction factor
Tenofovir disoproxil	1.0	---
Tenofovir disoproxil dimer impurity[1]	2.2	0.81

[1]Tetrakis(1-methylethyl)5,5'-(methylenebis{imino-9H-purine-6,9-diyl[(2R)-propane-1,2-dily]oxomethylene})bis-5-oxo-2,4,7-trioxa-5λ^5-phosphanonanoate.

Inject the reference solution. The test is not valid unless the column efficiency is not less than 3000 theoretical plates, the tailing factor is not more than 2.0 and the relative standard deviation for replicate injections is not more than 5.0 per cent.

Inject the reference solution and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to tenofovir disoproxil dimer impurity is not more than the area of the principal peak in the chromatogram obtained with the reference solution (0.15 per cent).

C. Determine by liquid chromatography (2.4.14).

Solvent mixture. Equal volumes of *water* and *methanol.*

Test solution. Dissolve 200 mg of the substance under examination in the solvent mixture and dilute to 5.0 ml with the solvent mixture.

Reference solution. A solution containing 0.00002 per cent w/v, each of, *9-propenyl adenine IPRS*(9-(prop-2-enyl)-9H-purin-6-amine) and *tenofovir impurity K IPRS* (9-(prop-1-enyl)-9H-purin-6-amine) in the solvent mixture.

Chromatographic system
— a stainless steel column 25 cm x 4.6 mm, packed with phenyl group bonded to porous silica (5 µm) (Such as X-Bridge phenyl),
— column temperature:35°,
— mobile phase: A. a 0.05 per cent w/v solution of *orthophosphoric acid* in *water,*
B. a mixture of 45 volumes of *acetonitrile* and 55 volumes of *methanol*,
— a gradient programme using the conditions given below,
— flow rate: 1 ml per minutes,
— spectrophotometer set at 260 nm,
— injection volume: 20 µl.

Time (in min)	Mobile phase A (per cent)	Mobile phase B (per cent)
0	96	4
15	83	17
20	20	80
25	20	80
30	96	4
35	96	4

Inject the reference solution. The test is not valid unless the column efficiency is not less than 1500 theoretical plates for 9-propenyl adenine peak and 4000 theoretical plates for tenofovir impurity K peak, the tailing factor is not more than 2.0 and the relative standard deviation for replicate injections is not more than 10.0 per cent for both the peaks.

Inject the reference solution and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to 9-propenyl adenine impurity and tenofovir impurity K, each of, is not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (5 ppm) and the sum of areas of 9-propenyl adenine impurity and tenofovir impurity K is not more than the area of the principal peak in the chromatogram obtained with the reference solution (5 ppm).

D. Determine by gas chromatography (2.4.13).

Blank. Transfer 2.0 ml of *N-methyl-2-pyrrolidinone* into a 20-ml headspace vial.

Test solution. Weigh and transfer 200 mg of the substance under examination to a 20-ml headspace vial and add 2.0 ml of *N-methyl-2-pyrrolidinone* and crimp cap with septum immediately.

Reference solution. A solution containing 0.00063 per cent v/v of *acetone*, 0.00064 per cent v/v of *isopropyl alcohol* and 0.0005per cent w/v of *chloromethyl isopropyl carbonate* in *N-methyl-2-pyrrolidinone.*Dilute 5.0 ml of the solution to 50.0 ml with *N-methyl-2-pyrrolidinone*. Transfer 2.0 ml of the solution to a 20-ml headspace vial and crimp cap with septum immediately.

Chromatographic system
- a capillary column 30 m x 0.32 mm, packed with 6 per cent cyanopropylphenyl and 94 per cent dimethylpolysiloxane (film thickness 1.8 µm) (Such as DB-624),
- temperature:
  column 38° for 10 minutes, 38° to 225° @ 12° per minute, and hold at 225° for 8 minutes,
  inlet port. 170° and detector. 250°,
- split ratio: 1:5,
- flow rate: 1 ml per minute using nitrogen as carrier gas,
- flame ionization detector,

Headspace conditions
- loop temperature: 110°,
- transfer-line temperature: 120°,
- equilibrium time: 45 minutes,
- pressurization time: 1.0 minutes,
- injection time: 1.0 minutes,
- injection volume: 1.0 ml.

Inject the reference solution. The test is not valid unless the resolution between the peaks due to acetone and isopropyl alcohol is not less than 1.5 and the relative standard deviation for replicate injections is not more than 15.0 per cent for each solvent peak.

Inject the reference solution and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to chloromethyl isopropyl carbonate is not more than 0.3 times the area of the corresponding peak in the chromatogram obtained with the reference solution (0.15 per cent).

Tenofovir Disoproxil Fumarate Tablets. Page 3746

Related substances

Change **to**: **Related substances**. Determine by liquid chromatography (2.4.14).

Buffer solution. Dissolve 1.41 g of *disodium hydrogen orthophosphate* in 1000 ml of *water*, adjusted to pH 5.5 with *orthophosphoric acid.*

Test solution. Disperse a quantity of the powdered tablets containing 0.2 g of tenofovir disoproxil in mobile phase A, with the aid of ultrasound for 10 minutes, with intermittent shaking and dilute to 500.0 ml with mobile phase A, filter.

Reference solution (a). A solution of *tenofovir disoproxil fumarate IPRS* containing 0.0002 per cent w/v solution of tenofovir disoproxil in the solvent mixture.

*Reference solution (b).*A solution containing 0.005 per cent w/v, each of, *tenofovir impurity IPRS, adenine impurity IPRS,* and *n-propyl impurity IPRS* and 0.0185 per cent w/v *tenofovir disoproxil dimer impurity IPRS* in mobile phase A. Transfer

1.5 ml of the solution to a 100-ml volumetric flask containing, 50.0 mg of *tenofovir disoproxil fumarate IPRS*, add 30.0 ml of mobile phase A, shake to dissolve and dilute to volume with mobile phase A.

*Reference solution (c).*Dilute 5.0 ml of reference solution (a) to 25.0 with mobile phase A.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (Such as YMC pack ODS AQ),
- column temperature: 35°,
- sample temperature: 4°,
- mobile phase: A. a mixture of 70 volumes of the buffer solution, 27.5 volumes of *methanol* and 2.5 volumes of *tertiary butanol*,
  B. a mixture of 30 volumes of the buffer solution, 67.5 volumes of *methanol* and 2.5 volumes of *tertiary butanol*,
- a gradient programme using the conditions given below,
- flow rate: 1 ml per minutes,
- spectrophotometer set at 260 nm,
- injection volume: 20 µl.

Time (in min)	Mobile phase A (per cent)	Mobile phase B (per cent)
0	100	0
2	100	0
30	0	100
45	0	100
50	100	0
60	100	0

Name	Relative retention time	Correction factor
Fumaric acid	0.11	---
Tenofovir impurity[1]	0.14	0.45
Adenine impurity[2]	0.16	0.25
Tenofovir isoproxil monoester impurity [3]	0.26	0.76
Tenofovir monosoproxil dimer (impurity F)	0.64	2.02
Tenofovir isoproxil isopropyl[4]	0.82	0.79
Tenofovir disoproxil	1.0	---
Tenofovir di-and monoproxil heterodimer (Tenofovir impurity I)	1.25	---
Tenofovir disoproxil dimer impurity[5]	1.72	1.14

[1](R)-1-(6-Amino-9H-purin-9-yl) propan-2-yloxy) methylphosphonic acid,
[2]9H-purin-6-amine,
[3](1-methylethyl) (8R)-9-(6-amino-9H-purin-9-yl)-5-hydroxy-8-methyl-5-oxo-2,4,7-trioxa-5λ^5-phosphanonanoate,
[4](1-methylethyl)(5RS,8R)-9-(6-amino-9H-purin-9-yl)-8-methyl-5-(1-methylethyl)-5-oxo-2,4,7-trioxa-5λ^5-phosphanonanoate,
[5]Tetrakis(1-methylethyl)5,5'-(methylenebis{imino-9H-purine-6,9-diyl[(2R)-propane-1,2-dily]oxomethylene})bis-5-oxo-2,4,7-trioxa-5λ^5-phosphanonanoate.

Inject reference solution (a), (b) and (c). The test is not valid unless the resolution between the peaks due to tenofovir impurity and adenine impurity is not less than 1.5in the chromatogram obtained with reference solution (b), the tailing factor is not more than 2.0, the relative standard deviation for replicate injections is not more than 5.0 per cent in the chromatogram obtained with reference solution (a) and the signal-to-noise ratio is not less 20 in the chromatogram obtained with reference solution (c).

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to tenofovir isoproxil monoester impurity is not more than 6 times the area of the principal peak in the chromatogram obtained with reference solution (a) (3.0 per cent),the area of any peak corresponding to tenofovir disoproxil dimer impurity and tenofovir monosoproxil dimer (impurity F), each of, is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent), the area of any peak corresponding to tenofovir impurity, adenine impurity and tenofovir di-and monoproxil heterodimer (tenofovir impurity I), each of, is not more than 0.4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent), the area of any peak corresponding to tenofovir isoproxil isopropyl impurity is not more than 0.6 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent),the area of any other secondary peak is not more than 0.4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent) and the sum of the areas of all the secondary peaks is not more than 8 times the area of the principal peak in the chromatogram

obtained with reference solution (a) (4.0 per cent).Ignore any peak due to fumaric acid and with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Theophylline. Page 3769

Identification

Change **to**: **Identification**

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *theophylline IPRS* or with the reference spectrum of theophylline.

B. In the Assay, the principal peak in the chromatogram obtained with test solution (b) corresponds to peak in the chromatogram obtained with reference solution (a).

Light absorption. Delete the requirement.

Related substances

Change **to**: **Related substances.** Determine by liquid chromatography (2.4.14).

Test solution (a). Dissolve 50 mg of the substance under examination in *water* and dilute to 50.0 ml with *water.*

Test solution (b). Dilute 5.0 ml of test solution (a) to 25.0 ml with *water.*

Reference solution (a). A 0.02 per cent w/v solution of *theophylline IPRS* in *water.*

Reference solution (b). A solution containing of 0.0001per cent w/v solution, each of, *caffeine IPRS, theophylline IPRS, theophylline related compound B IPRS, theophylline related compound C IPRS, theophylline related compound D IPRS, and theophylline related compound F IPRS* in *water.*

*Reference solution (c).*A 0.1 per cent w/v solution of *theophylline IPRS* and 0.0001 per cent w/v solution of *theophylline related compound F IPRS* in *water.*

Chromatographic system

- a stainless steel column 10 cm x 2.1 mm, packed with octadecylsilane bonded to porous silica (1.7 µm) (Such as Acquity UPLC BEH),
- column temperature: 40°,
- mobile phase: A. a buffer solution prepared by dissolving 770.8 mg of *ammonium acetate* in 800 ml with *water,* adjusted to pH 5.5 with *glacial acetic acid* and dilute to 1000 ml with *water,*
  B. *methanol,*
- a gradient programme using the conditions given below,
- flow rate: 0.4 ml per minute,
- spectrophotometer set at 270 nm and 220 nm,
- injection volume: 1 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	98	2
7	50	50
7.3	10	90
8.3	10	90
8.31	98	2
12	98	2

Name	Relative retention time
Theophylline related compound C[1]	0.36
Theophylline related compound B[2]	0.63
Theophylline related compound D[3]	0.69
Theophylline	1.0
Theophylline related compound F[4]*	1.09
Caffeine	1.20

* Included for establishing system suitability only,
[1] N-(6-Amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)formamide,
[2] 3-Methyl-1H-purine-2,6-dione,
[3] N-Methyl-5-(methylamino)-1H-imidazole-4-carboxamide hydrochloride monohydrate, (Theophyllidine);
[4] Etophylline; 7-(2-Hydroxyethyl)-1,3-dimethyl-3,7-dihydro-1H-purine-2,6-dione.

Inject reference solution (b) and (c). The test is not valid unless the resolution between the peaks due to theophylline and theophylline related compound F is not less than 1.5 in the chromatogram obtained with reference solution (c) and the relative standard deviation for replicate injections is not more than 3.0 per cent for each peak in the chromatogram obtained with reference solution (b).

Inject reference solution (b) and test solution (a). In the chromatogram obtained with test solution (a) at 270 nm, the area of any peak corresponding to theophylline related compound C, B, D and caffeine, each of, is not more than the area of corresponding peak in the chromatogram obtained with reference solution (b) (0.1 per cent). In the chromatogram obtained with test solution (a) at 220 nm, the area of any secondary peak other than theophylline related compound C, B, D and caffeine is not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent) and the sum of the areas of all the secondary peaks is not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent). Ignore any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Assay
Change **to**: **Assay**. Determine by liquid chromatography (2.4.14), as described under Related substances with the following modifications.
– spectrophotometer set at 270 nm

Inject reference solution (a) and (c). The test is not valid unless the resolution between the peaks due to theophylline and theophylline related compound F is not less than 1.5 in the chromatogram obtained with reference solution (c) and the relative standard deviation for replicate injections is not more than 1.0 per cent in the chromatogram obtained with reference solution (a).

Inject reference solution (a) and test solution (b).

Calculate the content of $C_7H_8N_4O_2$.

Insert at the end
Labelling. Label it to indicate whether it is anhydrous or hydrous.

Theophylline Injection. Page 3770

Identification. A
Change **to**: A. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with the reference solution.

Insert before **Bacterial endotoxins**
Related substances. Determine by liquid chromatography (2.4.14).

Test solution. Dilute a suitable volume of the injection containing 4 mg of Theophylline to 10.0 ml with *water.*

Reference solution (a). A solution containing 0.0004per cent w/v, each of, *theophylline related compound D IPRS* and 5-hydroxymethylfurfural in *water.* Dilute 1.0 ml of the solution to 10.0 ml with *water.*

*Reference solution (b).*A solution containing 0.0004per cent w/v, each of *theophylline IPRS and theophylline related compound D IPRS* in *water.* Dilute 1.0 ml of the solution to 10.0 ml with *water.*

Chromatographic system
– a stainless steel column 10 cm x 2.1 mm, packed with octadecylsilane bonded to porous silica (1.7 µm) (Such as Micro Bondapak C18),
– column temperature:40°,
– mobile phase: A. a buffer solution prepared by dissolving 771 mg of *ammonium acetate* in 800 ml with *water,* adjusted to pH 4.8 with *glacial acetic acid* and dilute to 1000 ml with *water,*
B. *methanol,*
– a gradient programme using the conditions given below,
– flow rate: 0.4 ml per minute,

– spectrophotometer set at 270 nm,
– injection volume: 2.5 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	93.5	6.5
2.5	93.5	6.5
5.0	10	90
5.1	93.5	6.5
7.0	93.5	6.5

Name	Relative retention time
Theophylline related compound D[1]	0.44
5-Hydroxymethylfurfural*	0.47
Theophylline	1.0

*5-Hydroxymethylfurfural is controlled in the Limit of 5-Hydroxymethylfurfural and Related substances test,
[1] N-Methyl-5-(methylamino)-1H-imidazole-4-carboxamide hydrochloride monohydrate, (Theophyllidine).

Inject reference solution (a) and (b). The test is not valid unless the resolution between the peaks due to theophylline related compound D and 5-hydroxymethylfurfural is not less than 1.1 in the chromatogram obtained with reference solution (a) and the relative standard deviation for replicate injections is not more than 5.0 per cent for both the peaks in the chromatogram obtained with reference solution (b).

Inject reference solution (b) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to theophylline related compound D is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent), the area of any other secondary peak is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent) and the sum of the areas of all the secondary peaks is not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent). Ignore any peak with an area less than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent).

Assay. *For theophylline —*
Change **to**:*For theophylline*— Determine by liquid chromatography (2.4.14).

Test solution. Dilute a volume of the injection containing 5 mg of Theophylline to 50.0 ml with *water.*

Reference solution. A 0.01 per cent w/v solution of *theophylline IPRS* in *water.*

Chromatographic system as described under Related substances with the following modification.
- injection volume: 1 µl

Inject the reference solution. The test is not valid unless the tailing factor is not more than 2.0 and the relative standard deviation for replicate injections is not more than 1.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_7H_8N_4O_2$ in the injection.

Theophylline Prolonged-release Tablets. Page 3771

Identification. A, line 2
Change **from**: the test solution
to: test solution (b)

Related substances
Change **to**: **Related substances**. Determine by liquid chromatography (2.4.14).

Solvent mixture. Dilute 138 ml of *ammonium hydroxide solution* to 1000 ml with *water.*

Test solution (a). Weigh and powder 20 Tablets. Disperse a quantity of powder containing 1 g of Theophylline in 75 ml of the solvent mixture and heat on a hot plate to just boiling with occasional stirring. Remove from the hot plate and sonicate for 5 minutes. Cool and dilute to 250.0 ml with *water,* filter.

Test solution (b). Dilute 5.0 ml of test solution (a) to 10.0 ml with *water.*

Reference solution (a). A 0.2 per cent w/v solution of *theophylline IPRS* in *water.*

Reference solution (b). A solution containing 0.0002 per cent w/v, each of, *theophylline IPRS and theophylline related compound D IPRS* in *water.*

Reference solution (c). Dilute 5.0 ml of reference solution (b) to 10.0 ml with *water.*

Chromatographic system

- a stainless steel column 10 cm x 2.1 mm, packed with octylsilane bonded to porous silica (1.7 µm) (Such as Acquity UPLC BEH),
- column temperature: 40°,
- mobile phase: A. a buffer solution prepared by dissolving 770.8 mg of *ammonium acetate* in 800 ml of *water,* adjusted to pH 5.5 with *glacial acetic acid* and dilute to 1000 ml with *water,*
  B. *methanol,*
- a gradient programme using the conditions given below,
- flow rate: 0.4 ml per minute,
- spectrophotometer set at 270 nm,
- injection volume: 1 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	93.5	6.5
2.5	93.5	6.5
5.0	10	90
5.1	93.5	6.5
7.0	93.5	6.5

Name	Relative retention time
Theophylline related compound D[1]	0.45
Theophylline	1.0

[1] N-Methyl-5-(methylamino)-1H-imidazole-4-carboxamide hydrochloride monohydrate, (Theophyllidine).

Inject reference solution (c). The test is not valid unless the relative standard deviation for replicate injections is not more than 5.0 per cent, for both the peaks.

Inject reference solution (b) and test solution (a). In the chromatogram obtained with test solution (a), the area of any peak corresponding to theophylline related compound D is not more than 4 times the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.2 per cent), the area of any other secondary peak is not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent) and the sum of the areas of all the secondary peaks is not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent). Ignore any peak with an area less than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent).

Assay

Change **to**: **Assay.** Determine by liquid chromatography (2.4.14), as described under Related substances with the following modifications.

Inject reference solution (a). The test is not valid unless the tailing factor is not more than 2.0 and the relative standard deviation for replicate injections is not more than 1.0 per cent.

Inject reference solution (a) and test solution (b).

Calculate the content of $C_7H_8N_4O_2$ in the tablets.

Tobramycin Sulphate. Page 5292

Para 2
Change **to**: Tobramycin Sulphate has a potency of not less than 634 mcg per mg and not more than 739 mcg per mg of tobramycin, $C_{18}H_{37}N_5O_9$.

Water
Change **to**: Not more than 7.0 per cent, determined on 0.3 g.

Assay. After chromatographic system, line 7
Change **to**: Calculate the content of $C_{18}H_{37}N_5O_9$.

Tolnaftate. Page 3826

Related substances. *Reference solution (a)*
Change **to:** *Reference solution (a).* A 0.01 per cent w/v solution of *tolnaftate IPRS* in *methanol.*

Insert before chromatographic system
Reference solution (c). A solution containing 0.001 per cent w/v of *tolnaftate IPRS* and 0.0001 per cent w/v of *tolnaftate impurity A IPRS* in *methanol.*

After chromatographic system, para 2
Change **to:** Inject reference solution (c). The test is not valid unless resolution between the peaks due to tolnaftate impurity A and tolnaftate is not less than 5.0.

Topiramate. Page 3833

Identification. B
Change **to**: B. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with the reference solution.

Topotecan Injection. Page 3836

Assay. After chromatographic system, line 2
Change **from**: relative standard deviation
to: relative standard deviation for replicate injections

Insert at the end
Labelling. The label states the strength in terms of equivalent amount of topotecan.

Tranexamic Acid. Page 3845

Related substances. Impurity table
Change **to**:

Name	Relative retention time	Correction factor
Tranexamic acid	1.0	---
Tranexamic acid related compound C[1]	1.1	0.005
Aminomethylbenzoic acid[2]	1.3	0.006
cis-Tranexamic acid[3]	1.5	1.21
Tranexamic acid impurity E[4]	1.7	0.3
Ditranexamic acid amine[5]	2.1	---

[1](RS)-4-(Aminomethyl)cyclohex-1-enecarboxylic acid,
[2]4-(Aminomethyl)benzoic acid.
[3] *cis*-4-(Aminomethyl)cyclohexanecarboxylic acid.
[4](1r,4r)-4-{[(aminomethyl)cyclohexane-1-carboxamido]methyl}cyclohexane-1-carboxylic acid,
[5]*trans,trans*-4,4'-[Iminobis(methylene)]dicyclohexanecarboxylic acid.

Lastpara, line 10 and 11
Change **to**: obtained with reference solution (a) (0.2 per cent),the area of any peak corresponding to tranexamic acid impurity E is not more than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent), the area of

Travoprost Eye Drops. Page 3850

pH. Change **to**:

pH (2.4.24). 5.5 to 6.5; If labelled to contain polyquarternium-1 as a preservative, 6.4 to 7.0; and if labelled to contain zinc chloride as an ingredient, 5.5 to 5.9.

Insert at the end
Labelling. If the eye drops are formulated with polyquarternium-1 as a preservative, it is so labelled. If the eye drops are formulated with zinc chloride as an ingredient, it is so labelled

Trimetazidine Hydrochloride. Page 3872

Related substances. *Reference solution*
Change **to:** *Reference solution (a).* A 0.0004 per cent w/v solution of *trimetazidine hydrochloride IPRS* in *water.*

Reference solution (b). Dissolve 20.0 mg of *trimetazidine for system suitability IPRS* in *water* and dilute to 5.0 ml with *water.*

Reference solution (c). Dilute 5.0 ml of reference solution (a) to 10.0 ml with *water.*

After chromatographic system, para 2 and 3
Change **to:**

Name	Relative retention time	Correction factor
Trimetazidine impurity D[1]	0.2	---
Trimetazidineimpurity C[2]	0.4	0.37
Trimetazidine impurity H[3]	0.6	---
Trimetazidine impurity A[4] and I[5]	0.9	---
Trimetazidineimpurity E[6]	0.95	---
Trimetazidine (Retention time: about 25 minutes)	1.0	---
Trimetazidine impurity F[7]	1.4	0.71
Trimetazidine impurity B[8]	1.8	0.55

[1](2,3,4-trimethoxyphenyl)methanol,
[2]2,3,4-trimethoxybenzaldehyde,
[3]ethyl 4-(2,3,4-trimethoxybenzyl)piperazine-1-carboxylate,
[4]1-(3,4,5-trimethoxybenzyl)piperazine,
[5]1-methyl-4-(2,3,4-trimethoxybenzyl)piperazine (N-methyltrimetazidine),
[6]1-(2,4,5-trimethoxybenzyl)piperazine,
[7]1-(2,4,6-trimethoxybenzyl)piperazine,
[8]1,4-bis(2,3,4-trimethoxybenzyl)piperazine.

Inject reference solution (b) and (c). The test is not valid unless the peak-to-valley ratio (*Hp/Hv*) is not less than 3.0, where *Hp* isthe height above the baseline of the peak due to trimetazidine impurity E and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the principal peakin the chromatogram obtained with referencesolution (b) and the signal-to-noise ratio is not less than 10 for theprincipal peak in the chromatogram obtained with referencesolution (c).

Inject reference solution (a), (c) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to trimetazidine impurity A, B, C, D, E, F, H and I, each of, is not morethan the area of the principal peak in thechromatogram obtained with reference solution(a) (0.1 per cent), the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtainedwith reference solution (a) (0.1 per cent) and the sum of the areas of all the secondary peaks is not more than twice thearea of the principal peak in the chromatogram obtained withreference solution(a) (0.2 per cent). Ignore any peak with an area less than the area of the principal peak in thechromatogram obtained with reference solution(c) (0.05 per cent).

Tubocurarine Chloride. Page 3888

Sulphated ash
Change **from**: Not more than 0.25 per cent, determined on 0.2 g.
to: Not more than 0.25 per cent.

Ursodeoxycholic Acid. Page 3900

Impurity C. Change **to:**
Impurity C. Determine by liquid chromatography (2.4.14).

Buffer solution. A solution prepared dissolving 0.8 g of *sodium dihydrogen orthophosphate* in 1000 ml of *water*, adjusted to pH 3.0 with *dilute orthophosphoric acid.*

Solvent mixture A.47 volumes of the buffer solution, 34 volumes of *methanol* and 25 volumes of *acetonitrile*.

Solvent mixture B.80 volumes of solvent mixture A and 20 volumes of *methanol*.

Test solution. Dissolve 0.5 g of the substance under examination in 5 ml of *methanol*, add 30 ml of solvent mixture B with the aid of ultrasound for 15 minutes and dilute to 50.0 ml with solvent mixture B.

Reference solution. A 0.01 per cent w/v solution of *lithocholic acid (impurity C) IPRS* in *methanol.* Dilute 1.0 ml of the solution to 10.0 ml with solvent mixture B.

Chromatographic system
– a stainless steel column 10 cm x 2.1 mm, packed with octadecylsilane bonded to porous silica (3µm) (Such as Inertsil ODS 3),
– column temperature: 40˚,
– mobile phase: a mixture of 55 volumes of buffer solution and 45 volumes of *acetonitrile*,
– flow rate: 0.6 ml per minute,
– refractometer detector, maintained at 40˚,
– injection volume: 100 µl.

Inject the reference solution. The test is not valid unless the column efficiency is not less than 2000 theoretical plates, the tailing factor is not more than 2.0 and the relative standard deviation for replicate injections is not more than 10.0 per cent.

Inject the reference solution and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to impurity C is not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (0.1 per cent).

Related substances
Change **to**: **Related substances.** Determine by liquid chromatography (2.4.14).

Solvent mixture. 10 volumes of *methanol* and 90 volumes of the mobile phase.

Test solution. Dissolve 60 mg of the substance under examination in the solvent mixture and dilute to 20.0 ml with the solvent mixture.

Reference solution (a). A 0.003 per cent w/v solution of *ursodeoxycholic acid IPRS* in the solvent mixture. Dilute 1.0 ml of the solution to 10.0 ml with the solvent mixture.

Reference solution (b). A solution containing 0.00003 per cent w/v of *ursodeoxycholic acid impurity H IPRS*, 0.0003 per cent w/v of *ursodeoxycholic acid impurity A IPRS* and 0.3 per cent w/v of *ursodeoxycholic acid IPRS* in the solvent mixture.

Chromatographic system
– a stainless steel column 25 cm x 4.6 mm, packed with endcapped octadecylsilane bonded to porous silica (5 µm),
– column temperature: 40˚,
– mobile phase: a mixture of 30 volumes of *acetonitrile*, 37 volumes of a 0.078 per cent w/v solution of *sodium dihydrogen phosphate*, adjusted to pH 3.0 with *orthophosphoric acid* and 40 volumes of *methanol*,
– flow rate: 0.8 ml per minute,
– refractometer detector, maintained at 35˚,
– injection volume: 150 µl.

Name	Relative retention time
Ursodeoxycholic acid impurity H[1]	0.9
Ursodeoxycholic acid (Retention time: about 14 minutes)	1.0
Ursodeoxycholic acid impurity A[2]	2.8

[1]3β,7β -dihydroxy-5β -cholan-24-oic acid,
[2]3α,7α -dihydroxy-5β-cholan-24-oic acid (chenodeoxycholic acid).

Inject reference solution (b) to identify the peaks due to ursodeoxycholic acid, impurity A and H.

Inject reference solution (b). The test is not valid unless the resolution between the peaks due to impurity H and ursodeoxycholic acid is not less than 1.5.

Inject reference solution (a) and the test solution. Run the chromatogram 4 times the retention time of the principal peak, the area of any peak corresponding toursodeoxycholic impurity A is not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent), the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent) and the sum of areas of all the secondary peaks is not more than 15 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.5 per cent). Ignore any peak with an area less than
0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Ursodeoxycholic Acid Tablets. Page 3902

Dissolution. Lines 2 to 5
Change **to:** Medium. 900 ml of phosphate buffer prepared by dissolving6.8 g of *potassium dihydrogenphosphate* and 1.9 g of *sodium hydroxide* in 850 ml of *water,* adjusted to pH 8.0 with *2 M sodium hydroxide* or *2 M hydrochloric acid* and dilute to 1000 ml with *water.*
Speed and time.75 rpm and 45 minutes.

Insert after chromatographic system
Inject the reference solution. The test is not valid unless the column efficiency is not less than 1600 theoretical plates, the tailing factor is not more than 2.0 and the relative standard deviation for replicate injections is not more than 2.0 per cent.

Last line
Change **from:** 75 per cent
to:80 per cent

Insert before **Related substances**
Impurity C. Determine by liquid chromatography (2.4.14).

Buffer solution. A solution prepared dissolving 0.8 g of *sodium dihydrogen orthophosphate* in 1000 ml of *water*,adjusted to pH 3.0 with *dilute orthophosphoric acid.*

Solvent mixture A.47 volumes of the buffer solution, 34 volumes of *methanol* and 25 volumes of *acetonitrile*.

Solvent mixture B.80 volumes of solvent mixture A and 20 volumes of *methanol*.

Test solution. Disperse a quantity of powdered tablets containing 0.5 g of ursodeoxycholic acid in 5 ml of *methanol*, add 30 ml of solvent mixture B with the aid of ultrasound for 15 minutes and dilute to 50.0 ml with solvent mixture B.

Reference solution. A 0.01 per cent w/v solution of *lithocholic acid (impurity C) IPRS* in *methanol.* Dilute 1.0 ml of the solution to 10.0 ml with solvent mixture B.

Chromatographic system
– a stainless steel column 10 cm x 2.1 mm, packed with octadecylsilane bonded to porous silica (3µm) (Such as Inertsil ODS 3),
– column temperature: 40˚,
– mobile phase: a mixture of 55 volumes of buffer solution and 45 volumes of *acetonitrile*,
– flow rate: 0.6 ml per minute,
– refractometer detector, maintained at 40˚,
– injection volume: 100 µl.

Inject the reference solution. The test is not valid unless the column efficiency is not less than 2000 theoretical plates, the tailing factor is not more than 2.0 and the relative standard deviation for replicate injections is not more than 10.0 per cent.

Inject the reference solution and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to impurity C is not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (0.1 per cent).

Related substances
Change **to**: **Related substances.** Determine by liquid chromatography (2.4.14).

Solvent mixture. 20 volumes of *methanol* and 80 volumes of mobile phase.

Test solution. Disperse a quantity of the powdered tablets containing 0.25 g of Ursodeoxycholic acid in the solvent mixture with the aid of ultrasound for 15 minutes and dilute to 50.0 ml with the solvent mixture and filter.

Reference solution (a). A 0.0025 per cent w/v solution of *ursodeoxycholic acid IPRS* in the solvent mixture.

Reference solution (b). A solution containing 0.5 per cent w/v of *ursodeoxycholic acid IPRS*, 0.0025 per cent w/v *ursodeoxycholic acid impurity F IPRS (7-ketolithocholic acid)*, 0.0055 per cent w/v of *ursodeoxycholic acid impurity A IPRS (chenodeoxycholic acid)* in the solvent mixture.

Reference solution (c). Dilute 1.0 ml of the reference solution (a) to 10.0 ml with the solvent mixture.

Chromatographic system
– a stainless steel column 10 cm x 2.1 mm, packed with octadecylsilane bonded to porous silica (3 µm), (Such as Uptisphere HDO C_{18}),
– column temperature: 40˚,
– mobile phase: a mixture of 25 volumes of *acetonitrile*, 34 volumes of *methanol* and 47 volumes of a buffer solution prepared by dissolving 0.8 g of *sodium dihydrogen orthphosphosphate dihydrate* in 1000 ml of *water*, adjusted to pH 3.0 with *orthophosphoric acid,*
– flow rate: 0.6 ml per minute,
– refractometer detector, maintained at 40˚,
– injection volume: 8 µl.

Name	Relative retention time
Ursodeoxycholic acid (Retention time: about 5 minutes)	1.0
Ursodeoxycholic acid impurity F[1]	1.3
Ursodeoxycholic acid impurity A[2]	2.8

[1]7-ketolithocholic acid
[2]chenodeoxycholic acid

Inject reference solution (b) to identify the peaks due to ursodeoxycholic acid, impurity A and F.

Inject reference solution (b). The test is not valid unless the resolution between the peaks due to ursodeoxycholic acid and ursodeoxycholic acid impurity F is not less than 2.0.

Inject reference solution (a), (c) and the test solution. Run the chromatogram 5 times the retention time of the principal peak, the area of any peak corresponding to ursodeoxycholic acid impurity A is not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.5 per cent), the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent) and the sum of areas of all the secondary peaks is not more than 4.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (2.1 per cent). Ignore any peak with an area less than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.05 per cent).

Valacyclovir Tablets. Page 3909

Related substances. *Test solution,* line 2
Change **from**: Valacyclovir Hydrochloride
to: valacyclovir

Reference solution (a)
Change **from**: A 0.01 per cent w/v solution of v*alacyclovir hydrochloride IPRS* in the solvent mixture.
to: A solution of v*alacyclovir hydrochloride IPRS* containing 0.01 per cent w/v of valacyclovi*r* in the solvent mixture.

Vancomycin Hydrochloride. Page 3921

Identification
Change **to**: A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *vancomycin hydrochloride IPRS* or with the reference spectrum of vancomycin hydrochloride.

B. In the test for Vancomycin B, the principal peak in the chromatogram obtained with test solution (a) corresponds to that in the chromatogram obtained with the reference solution.

C. It gives reaction (A) of chlorides (2.3.1).

Vancomycin Capsules. Page 3922

Identification

Change **to**: **Identification**
Disperse the contents of capsules containing 150 mg of vancomycin in about 20 ml of *chloroform*, filter the solution. Rinse the filter and residue with *chloroform*. Dry the residue in a vacuum at 60° for 1 hour.
On the residue, determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *vancomycin hydrochloride IPRS* or with the reference spectrum of vancomycin hydrochloride.

Insert before **Water**
Vancomycin B. Not less than 80 per cent.

NOTE- Prepare the solutions immediately before use.

Determine by liquid chromatography (2.4.14).

Buffer solution. A 0.2 per cent v/v solution of *triethylamine* in *water,* adjusted to pH 3.2 with *orthophosphoric acid.*

Test solution. Shake a quantity of the capsule contents containing 1,000,000 IU of Vancomycin with 100 ml of mobile phase A, at a temperature between 8° to 15° for 1 hour or until the capsule contents have dissolved (for a maximum of 2 hours). Filter the resulting solution through a 0.45-µm filters and then through a 0.22-µm filter and further dilute with mobile phase A to produce a solution containing 2,000 IU of Vancomycin per ml.

Reference solution (a). Dilute 1.0 ml of the test solution to 25.0 ml with mobile phase A.

Reference solution (b). Dilute 5.0 ml of reference solution (a) to 200.0 ml with mobile phase A.

Reference solution (c). Heat a 0.05 per cent w/v solution of *vancomycin hydrochloride IPRS* in *water* at 65° for 24 hours and allow to cool.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (Such as LiChrospher 100 RP-18),
- mobile phase: A. a mixture of 92 volumes of buffer solution, 7 volumes of *acetonitrile* and 1 volume of *tetrahydrofuran,*
  B. a mixture of 70 volumes of buffer solution, 29 volumes of *acetonitrile* and 1 volume of *tetrahydrofuran*,
- a gradient programme using conditions given below,
- flow rate: 1 ml per minute,
- spectrophotometer set at 280 nm,
- injection volume: 20 µl.

Time (in min)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	100	0
13	100	0
21	0	100
25	0	100
35	100	0
40	100	0

Inject reference solution (a), (b) and (c). The test is not valid unless the resolution between the two principal peaks is not less than 5.0 in the chromatogram obtained with reference solution (c), the tailing factor is not more than 1.6 for vancomycin peak in the chromatogram obtained with reference solution (a) and the signal-to-noise ratio is not less than 5 for principal peak in the chromatogram obtained with reference solution (b).

Calculate the percentage content of vancomycin B hydrochloride using the following expression:

$$\frac{A_b \text{X } 100}{A_b + \left(\frac{A_t}{25}\right)}$$

Where,

A_b= area of the peak corresponding to vancomycin B in the chromatogram obtained with reference solution (a);

A_t= sum of the areas of the peaks corresponding to impurities in the chromatogram obtained with the test solution.

Related substances. Determine by liquid chromatography (2.4.14), as described under Vancomycin B with the following modifications.

Inject reference solution (a), (b) and (c). The test is not valid unless the resolution between the two principal peaks is not less than 5.0 in the chromatogram obtained with reference solution (c), the tailing factor is not more than 1.6 for vancomycin peak in the chromatogram obtained with reference solution (a) and the signal-to-noise ratio is not less than 5 for principal peak in the chromatogram obtained with reference solution (b).

Inject reference solution (b) and the test solution. In the chromatogram obtained with the test solution, the content of one secondary impurity is not more than 5.0 per cent, the content of one another secondary impurity is not more than 4.0 per cent and sum of all the secondary impurities is not more than 20.0 per cent. Ignore any peak with an area less than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent).

Calculate the percentage content of each impurity using the following expression:

$$\frac{\left(\frac{A_i}{25}\right) \text{X } 100}{A_b + \left(\frac{A_t}{25}\right)}$$

Where,

A_i =area of an impurity peak in the chromatogram obtained with the test solution,

A_b= area of the peak corresponding to vancomycin B in the chromatogram obtained with reference solution (a),

A_t= sum of the areas of the peaks corresponding to impurities in the chromatogram obtained with the test solution.

Sterile Water for Inhalation. Page 3966

Oxidizable substances. Delete the requirement

Total organic carbon. Line 3
Delete "Alternately perform the test for Oxidizable substances."

Sterile Water for Injections. Page 5301

Total Organic Carbon or Oxidisable Substances.
Change **to**: **Total organic carbon** (2.4.30). Meets the requirement of the test.

Nicotinic Acid. Page 4102

Para 2

Change **to:** Nicotinic Acid contains not less than 98.0 per cent and not more than 102.0 per cent of $C_6H_5NO_2$, calculated on the dried basis.

Identification. C

Change **to**: C. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with reference solution (a).

Related substances. Change **to**:

Related substances. Determine by liquid chromatography (2.4.14).

Test solution. Weigh and transfer 0.12 g of the substance under examination in 10-ml volumetric flask, add 0.2 ml of 10 per cent v/v of *ammonium hydroxide solution* and dilute to volume with mobile phase A.

Reference solution (a).A 0.0012 per cent w/v solution of *nicotinic acid IPRS* in mobile phase A.

Reference solution (b).A solution containing 0.0012 per cent w/v, each, of *6-methylnicotinic acid IPRS*, *6,6-dinicotinic acid IPRS* and *pyridine* in mobile phase A.

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (4 µm) (Such as synergy hydro-RP),
- column temperature 15º,
- mobile phase: A. a 0.06 per cent w/v solution of *glacial acetic acid* in *water*, adjusted to pH5.6with 10per cent v/v of *ammonium hydroxide solution*,
  B. a mixture of equal volumes of *acetonitrile* and *methanol*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 250 nm,
- injection volume: 10 µl.

Time (in min)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	100	0
10	100	0
30	20	80
35	20	80
36	100	0
48	100	0

Name	Relative retention time
Isocinchomeronic acid	0.38
6-Hydroxynicotinic acid	0.63
Isonicotinic acid	0.92
Nicotinic acid	1.00
6-Methylnicotinic acid	2.61
6,6-Dinicotinic acid	2.68
5-Nitronicotinic acid	2.76
Pyridine	3.76
3- Nitropyridine	3.83
3,5-Dinitropyridine	4.03
3-Ethylpyridine	4.72
5-Ethyl-2-methylpyridine	5.00

The relative retention times with reference to 6-methylnicotinic acid, for 6,6'-dinicotinic acid and pyridine are 1.03 and 1.4, respectively in reference solution (b).

Inject reference solution (a) and (b). The test is not valid unless the resolution between the peaks due to 6-methylnicotinic acid and 6,6-dinicotinic acid is not less than 1.5 in the chromatogram obtained with reference solution (b) and the relative standard deviation for replicate injections is not more than 10.0 per cent in the chromatogram obtained with reference solution (a).

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to isocinchomeronic acid, 6-hydroxynicotinic acid, isonicotinic acid, 6-methylnicotinic acid, 6,6-dinicotinic acid, 5-nitronicotinic acid, pyridine, 3-nitropyridine, 3,5-dinitropyridine, 3-ethylpyridine, and 5-ethyl-2-methylpyridine, each of, is not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent), the area of any other secondary peak is not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent) and the sum of the areas of all the secondary peaks is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent). Ignore any peak with an area less than 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.03 per cent).

Assay. Change **to**:
Assay. Determine by liquid chromatography (2.4.14).

Solvent mixture. 82 volumes of *methanol* and 18 volumes of *water*.

Test solution. Dissolve 25 mg of the substance under examination in the solvent mixture and dilute to 100.0 ml with the solvent mixture.
Reference solution (a).A 0.025 per cent w/v solution of *nicotinic acid IPRS* in the solvent mixture.

Reference solution (b).A solution containing 0.025per cent w/v of *nicotinic acid IPRS,*0.005per cent w/v of *6-hydroxynicotinic acid IPRS* and 0.01 per cent w/v of *pyridine* in the solvent mixture.

Chromatographic system

- a stainless steel column 15 cm x 4.6 mm, packed with monomolecular layer of aminopropylsilane bonded to porous silica (5 µm) (Such as purospher- Star NH_2),
- mobile phase: a mixture of 82 volumes of *methanol* and 18 volumes of *water*, adjusted to pH3.15with*glacialacetic acid*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 260 nm,
- injection volume: 25 µl.

The relative retention time with reference to nicotinic acid for pyridine and 6-hydroxynicotinic is about 0.14 and 0.64 respectively in reference solution (b).

Inject reference solution (a) and (b). The test is not valid unless the resolution between the peaks due to pyridine and 6-hydroxynicotinic acid is not less than 1.5 and between the peaks due to 6-hydroxynicotinic acid and nicotinic acid is not less than 1.5 in the chromatogram obtained with reference solution (b) and the relative standard deviation for replicate injections is not more than 2.0 per cent in the chromatogram obtained with reference solution (a).

Inject reference solution (a) and the test solution.

Calculate the content of $C_6H_5NO_2$.

VETERINARY PRODUCTS

Inositol. Page 4883

Change **to**: **Inositol**

Category. Vasodilator

For Description, Identification and Tests refer to IP Volume III.

Meloxicam Injection. Page 4897

Related substances

Change **to: Related substances**. Determine by liquid chromatography (2.4.14).

Test solution. To a volume of the injection containing 40 mg Meloxicam, add 0.3 ml of *0.4M sodium hydroxide* and dilute to 10.0 ml with *methanol (40 per cent)*.

Reference solution (a). Add 0.3 ml of *0.4M sodium hydroxide* to 40 mg of *meloxicam IPRS* and dilute to 10.0 ml with *methanol* (*40 per cent*).Dilute 1.0 ml of the solution to 100.0 ml with *methanol* (*40 per cent*).

Reference solution (b). Add 0.3 ml of *0.4M sodium hydroxide* to 40 mg of *meloxicam IPRS*, 2 mg of *meloxicam impurity A IPRS* (ethyl 4-hydroxy-2-methyl-2H-1,2-benzothiazine-3-carboxylate 1,1-dioxide) and 2 mg of *meloxicam impurity B IPRS* (5-methylthiazol-2-amine) and dilute to 10.0 ml with *methanol* (*40 per cent*).

Chromatographic system

- a stainless steel column 10 cm x 4.0 mm, packed with octadecylsilane bonded to porous silica (10 µm) (Such as Kromasil 100),
- mobile phase: A. a 0.1 per cent w/v solution of *potassium dihydrogen phosphate*, adjusted to pH 6.0 with *2 M sodium hydroxide*,
  B. *methanol,*
- flow rate: 1 ml per minute,
- a gradient programme using the conditions given below,
- spectrophotometer set at 260 nm and 350 nm,
- injection volume: 10 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	60	40
2.5	60	40
12	30	70
25	30	70
26	60	40
60	40	30

Inject reference solution (b) at 260 nm and 350 nm. The test is not valid unless the resolution between the peaks due to meloxicam and meloxicam impurity A is not less than 3.0 at 350 nm and meloxicam impurity B and meloxicam is not less than 3.0 at 260 nm.

Inject reference solution (a) and the test solution at 350 nm. In the chromatogram obtained with the test solution, the area of any peak corresponding to meloxicam impurity A, multiplied with correction factor 2.0 is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent).

Inject reference solution (a) and the test solution at 260 nm. In the chromatogram obtained with the test solution, the area of any peak corresponding to meloxicam impurity B is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) at 350 nm (2.0 per cent).

The area of any other secondary peak, at the wavelength giving the higher value for the impurity, is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) at the same wavelength (1.0 per cent).

The sum of all the impurities is not more than 3.5 per cent. Ignore any peak with an area less than 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (a) at the same wavelength (0.3 per cent).

Assay

Change **to: Assay**. Determine by liquid chromatography (2.4.14).

Test solution. To a volume of the injection containing 40 mg Meloxicam, add 0.3 ml of *0.4M sodium hydroxide* and dilute to 10.0 ml with *methanol (40 per cent)*. Dilute 1.0 ml of the solution to 10.0 ml with *methanol* (*40 per cent*).

Reference solution (a). Add 0.3 ml of *0.4M sodium hydroxide* to 40 mg of *meloxicam IPRS* and dilute to 10.0 ml with *methanol* (*40 per cent*). Dilute 1.0 ml of the solution to 10.0 ml with *methanol* (*40 per cent*).

Reference solution (b). Add 0.3 ml of *0.4M sodium hydroxide* to 40 mg of *meloxicam IPRS,* 2 mg of *meloxicam impurity A IPRS* (ethyl 4-hydroxy-2-methyl-2H-1,2-benzothiazine-3-carboxylate 1,1-dioxide) and 2 mg of *meloxicam impurity B IPRS* (5-methylthiazol-2-amine) and dilute to 10.0 ml with *methanol* (*40 per cent*).

Use chromatographic system as described under Related substances with the following modification.

– spectrophotometer set at 350 nm,

Inject reference solution (b). The test is not valid unless the resolution between the peaks due to meloxicam and meloxicam impurity A is not less than 3.0.

Inject reference solution (a) and the test solution.

Calculate the content of $C_{14}H_{13}N_3O_4S_2$ in the injection.