Colistimethate Injection

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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 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.	

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Change **to:** **Colistimethate for Injection**

Colistimethate Sodium for Injection

Colistimethate for Injection is a sterile material consisting of Colistimethate Sodium with or without excipients. It is supplied in a sealed container.

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Colistimethate Sodium for Injection contains not less than 95.0 per cent and not more than 115.0 per cent of the stated amount of colistimethate sodium.

Usual strengths. 1 million IU and 2 million IU per vial.

Identification

A. In the Composition, the peaks due to CMS E1ASM8, CMS E1ASM6, CMS E1ASM4, CMS E2ASM8, CMS E2ASM6 and CMS E2ASM4 in the chromatogram obtained with the test solution corresponds to the peaks in the chromatogram obtained with reference solution (a).

B. It gives reaction (b) of sodium salts (2.3.1).

Tests

pH (2.4.24). Dissolve a quantity in *carbon dioxide-free water* to obtain a solution containing 125,000 IU per ml. The pH of the solution, measured after 30 minutes of preparation, is 6.5 to 8.5

Free colistin. Dissolve a quantity containing 1,000,000 IU in 3 ml of *water*, add 0.1 ml of a 10.0 per cent w/v solution of *silicotungstic acid* and allow to stand for 10 to 20 seconds. The solution is not more opalescent than opalescence standard OS2 (2.4.1).

Composition. Determine by liquid chromatography (2.4.14).

NOTE- Store all the solutions at 5°.

Buffer solution. A 0.78 per cent w/v solution of *sodium dihydrogen phosphate dihydrate,* adjusted to pH 6.5 with *1M sodium hydroxide.*

Test solution. Dissolve a quantity of the contents of a sealed container in sufficient *water* to produce a solution containing 500,000 IU of Colistimethate Sodium per ml. Dilute 1.0 ml of the reconstituted solution to 20.0 ml with *methanol.*

Reference solution (a). Dissolve 10 mg of *colistimethate sodium for peak identification IPRS* in 0.25 ml of *water* and dilute to 5.0 ml with *methanol.*

Reference solution (b). Dissolve 5 mg of *E1 colistimethate sodium for peak identification IPRS* in 0.25 ml of *water* and dilute to 5.0 ml with *methanol.*

Reference solution (c). Dissolve 1.5 mg of *E2 colistimethate sodium for peak identification IPRS* in 0.25 ml of *water* and dilute to 5.0 ml with *methanol.*

Reference solution (d). Dilute 3.0 ml of reference solution (a) to 50.0 ml with *methanol.*

Chromatographic system
– a stainless steel column 15 cm × 2.1 mm, packed with end-capped, octadecylsilane bonded to porous silica (hybrid material) (1.7 µm) (Such as Waters Acquity UPLC CSH),

–column temperature: 30°,
–sample temperature: 5°,
–mobile phase: A. a mixture of 5 volumes of *acetonitrile* and 95 volumes of the buffer solution,
B. a mixture of 50 volumes of *acetonitrile* and 50 volumes of the buffer solution,
– a gradient programme using the conditions given below,
– flow rate: 0.3 ml per minute,
– spectrophotometer set at 210 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
10	68	32
35	53	47
36	80	20
44	80	20

Name	Relative retention time
CMS E2ASM8	0.22
CMS E1ASM8	0.39
CMS E2ASM6	0.71
CMS E1ASM6 (Retention time: about 13 minutes)	1.0
CMS E2ASM4	1.77
CMS E1ASM4	2.35

Inject reference solution (a) to identify the peaks due to CMS E1ASM6, CMS E2ASM8, CMS E1ASM8, CMS E2ASM6, CMS E2ASM4 and CMS E1ASM4.

Inject reference solution (a). The difference in the retention times between two consecutive injections of reference solution (a) is less than 0.1 minutes and the drift in the retention time of CMS E1ASM6 from start to the end of the sequence is less than 0.5 minutes.

Inject reference solution (a) and (d). The test is not valid unless the column efficiency is not less than 50000 theoretical plates calculated for the peak due to CMS E1ASM6, the peak-to-valley ratio is not less than 1.2, where *Hp* = height above the baseline of the peak with a relative retention of about 2.37 and *Hv* = height above the baseline of the lowest point of the curve separating this peak from the peak due to CMS E1ASM4 in the chromatogram obtained with reference solution (a). and the signal-to-noise ratio is not less than 50 for the peak due to CMS E1ASM6 in the chromatogram obtained with reference solution (d).

Inject the test solution. Integrate all peaks present at more than 0.05 per cent to determine the total peak area. Calculate the percentage of colistimethate sodium components in the injection by area normalization method.

Inject the test solution. The area of any peak corresponding to CMS E1ASM8 is not less than 5.0 per cent and not more than 9.5 per cent, the area of any peak corresponding to CMS E1ASM6 is not less than 6.5 per cent and not more than 9.5 per cent, the area of any peak corresponding to CMS E1ASM4 is not less than 2.0 per cent and not more than 5.0 per cent, the area of any peak corresponding to CMS E2ASM8 is not less than 0.5 per cent and not more than 2.0 per cent, the area of any peak corresponding to CMS E2ASM6 is not less than 0.5 per cent and not more than 2.5 per cent, the area of any peak corresponding to CMS E2ASM4 is not more than 1.5 per cent and the sum of the areas of the peaks related to CMS E1 and CMS E2 is not less than 77.0 per cent. Ignore any peak with an area less the 0.5 per cent, calculated by area normalization method.

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

Inject reference solution (b) and (c) to identify the peaks due to components of CMS E1 and CMS E2.

Inject the test solution. The area of any secondary peak is not more than 2.0 per cent and the sum of the areas of all the secondary peaks is not more than 7.0 per cent. Ignore any peak related to CMS E1 or CMS E2 and any peak with an area less the 0.5 per cent, calculated by area normalization method.

Loss on drying (2.4.19). Not more than 7.0 per cent, determined on 1.0 g by drying in an oven at 60° over *phosphorus pentoxide* at a pressure not exceeding 0.7 kPa for 3 hours.

Assay. Determine the weight of the contents of 10 containers as described under Uniformity of dosage units (2.5.4). Uniformity of weight, powders for parenteral administration.

Mix the contents of the 10 containers and carry out the microbiological assay of antibiotics (2.2.10). The precision of the assay is such that the fiducial limits of error are not less than 95.0 per cent and more than 105.0 per cent of the estimated potency.

For a container of average content weight, the upper fiducial limit of error is not less than 95.0 per cent and the lower fiducial limit of error is not more than 115.0 per cent of the stated number of IU.

Storage. Store protected from light and moisture.

Labelling. The label of the sealed container states the total number of IU (units) contained in it.