Clomifene Citrate

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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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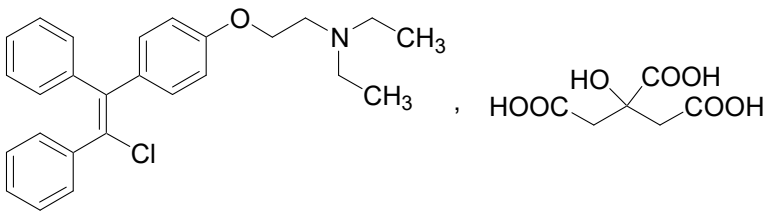
Change **to**: **Clomifene Citrate**

Clomiphene Citrate



$C_{26}H_{28}ClNO,C_6H_8O_7$ Mol. Wt. 598.1

Clomifene Citrate is Ethanamine,2-[4-(2-chloro-1,2-diphenylethenyl)phenoxy]-*N*,*N*-diethyl-,2-hydroxy-1,2,3-propane tricarboxylate (1:1); 2-[*p*-(2-Chloro-1,2-diphenylvinyl)phenoxy]triethylamine citrate (1:1)

Clomifene Citrate contains not less than 98.0 per cent and not more than 102.0 per cent of a mixture of the *E* and *Z*-isomers of $C_{26}H_{28}ClNO$, $C_6H_8O_7$, calculated on the anhydrous basis.

Category. Ovulation inducer.

Description. A white to pale yellow powder.

Identification

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *clomifene citrate IPRS* or with the reference spectrum of clomifene citrate.

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).

C. Dissolve about 5 mg in 5 ml of a mixture of 10 volumes of *acetic anhydride* and 50 volumes of *pyridine* and heat in a water-bath; a deep red colour is produced.

Tests

Related substances. Determine by liquid chromatography (2.4.14).

NOTE - Use low-actinic glassware for all solutions.

Buffer solution. A mixture of 40 volumes of *acetonitrile*, 60 volumes of *water* and 0.8 volume of *diethylamine*, adjusted to pH 6.2 with *orthophosphoric acid*.

Test solution. Dissolve 25 mg of the substance under examination in the buffer solution and dilute to 20.0 ml with the buffer solution.

Reference solution (a). A 0.0025 per cent w/v solution of *clomifene citrate IPRS* in the buffer solution.

Reference solution (b). A solution containing 0.125 per cent w/v of *clomifene citrate IPRS* and 0.0028 per cent w/v of *clomifene related compound A IPRS* in the buffer solution.

Chromatographic system

- a stainless steel column 10 cm x 4.6 mm, packed with octylsilane bonded to porous silica (2.6 µm) (Such as Kinetex C8),
- mobile phase: A. a mixture of 90 volumes of the buffer solution and 10 volumes of *water*,

B. buffer solution,

- a gradient programme using the conditions given below,
- flow rate: 1.5 ml per minute,
- spectrophotometer set at 233 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
3	100	0
23	0	100
33	0	100
33.5	100	0
40	100	0

Name	Relative retention time	Correction factor
Clomifene benzophenone analog[1]	0.10	1.96
Clomifene tritylphenone analog[2]	0.13	---
Clomifene keto analog[3]	0.33	---
Clomifene related compound A[4]	0.92	---
Clomifene Z-isomer	0.98	---
Clomifene E-isomer	1.0	---
2-Chloroclomifene[5]	1.57	---
2-Chloroclomifene[5]	1.63	---
4-Chloroclomifene[6]	1.70	---
4-Chloroclomifene[6]	1.77	---
Deschloroclomifene chlorophenyl analog[7]	2.36	1.29
Deschloroclomifene chlorophenyl analog [7]	2.48	1.29
Benzyl clomifene[8]	2.67	1.35
Benzyl clomifene[8]	2.76	1.23

[1] {4-[2-(Diethylamino)ethoxy]phenyl}(phenyl)methanone,
[2] 2,2-Bis{4-[2-(diethylamino)ethoxy]phenyl}-1,2-diphenylethanone,
[3] 2-{4-[2-(Diethylamino)ethoxy]phenyl}-1,2-diphenylethan-1-one,
[4] (*E*,*Z*)-2-[4-(1,2-Diphenylvinyl)phenoxy]-*N*,*N*-diethylethanamine hydrochloride.
[5] (*E*,*Z*)-2-[2-Chloro-4-(2-chloro-1,2-diphenylvinyl)phenoxy]-*N*,*N*-diethylethan-1-amine,
[6] (*E*,*Z*)-2-{4-[2-Chloro-2-(4-chlorophenyl)-1-phenylvinyl]phenoxy}-*N*,*N*-diethylethan-1-amine,
[7] (*E*,*Z*)-2-{4-[1,2-Bis(4-chlorophenyl)vinyl]phenoxy}-*N*,*N*-diethylethan-1-amine,
[8] (*E*,*Z*)-2-{4-[1-(4-Benzylphenyl)-2-chloro-2-phenylvinyl]phenoxy}-*N*,*N*-diethylethan-1-amine.

Inject reference solution (a) and (b). The test is not valid unless the relative standard deviation for replicate injections is not more than 5.0 per cent from the sum of the peak areas of *E* and *Z* isomers in the chromatogram obtained with reference solution (a) and the peak-to-valley ratio between the height of the clomifene related compound A peak and the height of the valley between clomifene related compound A and clomifene is not less than 15 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 clomifene benzophenone analog, clomifene tritylphenone analog, clomifene keto analog, each of, is not more than 0.5 times the sum of the peak areas of *E* and *Z* isomers in the chromatogram obtained with reference solution (a) (1.0 per cent), the area of any peak corresponding to clomifene related compound A is not more than the sum of the peak areas of *E* and *Z* isomers in the chromatogram obtained with reference solution (a) (2.0 per cent), the sum of the areas of the geometric isomers corresponding to 2-chloroclomifene is not more than 0.5 times the sum of the peak areas of *E* and *Z* isomers in the chromatogram obtained with reference solution (a) (1.0 per cent), the sum of the areas of the geometric isomers corresponding to 4-chloroclomifene is not more than 0.5 times the sum of the peak areas of *E* and *Z* isomers in the chromatogram obtained with reference solution (a) (1.0 per cent), the sum of the areas of the geometric isomers corresponding to deschloroclomifene chlorophenyl analog is not more than 0.5 times the sum of the peak areas of *E* and *Z*

isomers in the chromatogram obtained with reference solution (a) (1.0 per cent), the area of any peak corresponding to benzyl clomifene at relative retention time 2.67, 2.76, each of, is not more than 0.075 times the sum of the peak areas of *E* and *Z* isomers in the chromatogram obtained with reference solution (a) (0.15 per cent), the area of any other secondary peak is not more than 0.05 times the sum of the peak areas of *E* and *Z* isomers 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 1.25 times the sum of the peak areas of *E* and *Z* isomers in the chromatogram obtained with reference solution (a) (2.5 per cent).

***Z*-isomer**. Not less than 30 per cent and not more than 50 per cent.

Determine by liquid chromatography (2.4.14), as described under Assay.

Calculate the content of Z-isomer [(*Z*)-2-[4-(2-chloro-1,2-diphenylethenyl)phenoxy]-*N*,*N*-diethylethanamine 2-hydroxy-1,2,3-propanetricarboxylate (1:1).

Water (2.3.43). Not more than 1.0 per cent, determined on 1.0 g.

Assay. Determine by liquid chromatography (2.4.14).

NOTE - Use low-actinic glassware for all solutions.

Test solution. Dissolve 25 mg of the substance under examination in the mobile phase and dilute to 50.0 ml with the mobile solution. Further dilute 1.0 ml of the solution to 10.0 ml with the mobile phase.

Reference solution (a). A 0.005 per cent w/v solution of *clomifene citrate IPRS* in the mobile phase.

Reference solution (b). A solution containing 0.0002 per cent w/v of *clomifene related compound A IPRS* and 0.005 per cent w/v of *clomifene citrate IPRS* in the mobile phase.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with butylsilane bonded to porous silica (5 µm) (Such as Vydac C4),
- mobile phase: a mixture of 55 volumes of *methanol*, 45 volumes of *water* and 0.3 volume of *triethylamine,* adjusted to pH 2.5 with *orthophosphoric acid,*
- flow rate: 1 ml per minute,
- spectrophotometer set at 233 nm,
- injection volume: 50 µl.

Name	Relative retention time
Clomifene related compound A[1]	0.9
Clomifene Z-isomer	1.0
Clomifene E-isomer	1.2

[1] (*E*,*Z*)-2-[4-(1,2-Diphenylvinyl)phenoxy]-*N*,*N*-diethylethanamine hydrochloride.

Inject reference solution (a) and (b). The test is not valid unless the resolution between the peaks due to clomifene related compound A and *Z*-isomer is not less than 1.0, *Z*-isomer and *E*-isomer is not less than 1.5 in the chromatogram obtained with reference solution (b), the column efficiency is not less than 2000 theoretical plates for *E*-isomer, the tailing factor is not more than 3.0 for *E*-isomer and the relative standard deviation for replicate injections is not more than 2.0 per cent for both *E*-isomer and *Z*-isomer in the chromatogram obtained with reference solution (a).

Inject reference solution (a) and the test solution.

Calculate the content of $C_{26}H_{28}ClNO,C_6H_8O_7$, from the sum of *Z*-isomer and *E*-isomer.

Storage. Store protected from light and moisture, at a temperature not exceeding 30°.