Pretomanid

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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. 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 arnd-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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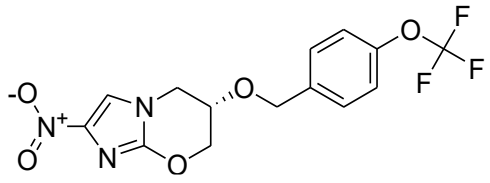
Pretomanid



$C_{14}H_{12}F_3N_3O_5$ Mol. Wt. 359.3

Pretomanid is (6*S*)-2-nitro-6-[[4-(trifluoromethoxy)phenyl]methoxy]-6,7-dihydro-5*H*-imidazo[2,1-b][1,3]oxazine.

Pretomanid contains not less than 98.0 per cent and not more than 102.0 per cent of $C_{14}H_{12}F_3N_3O_5$, calculated on the anhydrous and solvent free basis.

Category. Anti-tubercular.

Description. A white to off-white to yellow colour powder.

Identification

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

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.

Tests

Enantiomer purity. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve 25 mg of the substance under examination in *ethanol* with the aid of ultrasound and dilute to 50.0 ml with *ethanol*.

Reference solution (a). A 0.025 per cent w/v solution of *enantiomer of pretomanid IPRS* in *ethanol*. Dilute 3.0 ml of the solution to 10.0 ml with *ethanol*. Dilute 1.0 ml of the solution to 100.0 ml with *ethanol*. *[NOTE- Sonicate to dissolve, if necessary]*

Reference solution (b). A 0.05 per cent w/v solution of *pretomanid IPRS* in reference solution (a). *[NOTE- Sonicate to dissolve, if necessary]*

Chromatographic system
- a stainless steel column 25 cm × 4.6 mm, packed with cellulose tris(4-chloro-3-methylphenylcarbamate) bonded to porous silica (3 µm), (such as Chiralcel OX-3),
- column temperature: 35°,
- mobile phase: a mixture of 30 volumes of *ethanol,* 70 volumes of *n-heptane* and 0.1 volumes of *trifluoroacetic acid*,
- flow rate: 0.8 ml per minute,
- spectrophotometer set at 330 nm,
- injection volume: 20 µl.

Name	Relative retention time
Pretomanid	1.0

Enantiomer of pretomanid[1] 1.18

[1] (6R)-2-nitro-6-{[4-(trifluoromethoxy)benzyl]oxy)-6,7-dihydro-5*H*-imidazol2,l-b][1,3] oxazine

Inject reference solution (a) and (b). The test is not valid unless the resolution between the peaks due to pretomanid and enantiomer of pretomanid is not less than 2.5 in the chromatogram obtained with reference solution (b), the column efficiency is not less than 5000 theoretical plates; 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 (a).

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to enantiomer of pretomanid is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent).

Related substances. Determine by liquid chromatography (2.4.14).

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

Test solution. Dissolve 50 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.

Reference solution (a). A 0.0001 per cent w/v solution of *pretomanid IPRS* in the solvent mixture. *[NOTE- Sonicate to dissolve, if necessary]*

Reference solution (b). A solution containing 0.1 per cent w/v of *pretomanid IPRS* and 0.00015 per cent w/v of *meta isomer impurity IPRS* in the solvent mixture. *[NOTE- Sonicate to dissolve, if necessary]*

Chromatographic system
- a stainless steel column 10 cm × 4.6 mm, packed with octadecylsilane bonded to porous silica (3 µm), (such as Zodiac-C18),
- column temperature: 30°,
- mobile phase: A. dissolve 1.3 g of *potassium dihydrogen orthophosphate* in 1000 ml of *water*, adjusted to pH 2.0 with *dilute phosphoric acid*,
  B. *acetonitrile*,
- 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	65	35
16	60	40
20	30	70
30	30	70
35	65	35
40	65	35

Name	Relative retention time	Correction factor
Pretomanid dimer impurity[1]	0.63	0.85
Methoxy impurity[2]	0.67	1.09
Ortho isomer impurity [3]	0.84	1.43
Benzyloxy propanol impurity[4]	0.90	0.83
Meta isomer impurity [5]	0.94	1.25
Pretomanid	1.0	---
Benzyloxy propyl pivalate impurity[6]	1.52	1.11

[1](6S,6'S)-6,6'-{[4-(trifluoromethoxy)benzene-1,3 diyl]bis(methanediyloxy)}bis(2-nitro-6,7-dihydro-5*H*-imidazo[2,1-b] [1,3]oxazine),
[2](S)-3-(2-methoxy-4-nitro-1*H*-imidazol-l-yl)-2-{[4-(trifluoromethoxy)benzyl]oxy}propan-1-ol,
[3] (6S)-2-nitro-6-{[2-(trifluoromethoxy)benzyl]oxy}-6,7-dihydro-5*H*-imidazo[2,l-b]1,3}oxazine,
[4](2S)-3-(2-bromo-4-nitro-1*H*-imidazol-1-yl)-2-{[4-(trifluoromethoxy) benzyl] oxy} propan-1–ol,
[5](6S)-2-nitro-6-{[3-(trifluoromethoxy)benzyl]oxy}-6,7-dihydro-5*H*- imidazo[2,l-b]1,3} oxazine,
[6](2S)-3-(2-bromo-4-nitro-l*H*-imidazol-1-yl)-2-{[4-(trifluoromethoxy)benzyl]oxy}propyl 2,2-dimethylpropanoate.

Inject reference solution (a) and (b). The test is not valid unless the resolution between the peaks due to meta isomer impurity and pretomanid is not less than 1.5 in the chromatogram obtained with reference solution (b), the column efficiency is not less than 10000 theoretical plates, 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 (a).

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to pretomanid dimer impurity, methoxy impurity, ortho isomer impurity, benzyloxy propanol impurity, meta isomer impurity and benzyloxy propyl pivalate impurity, 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) and 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 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 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Sulphated ash (2.3.18). Not more than 0.14 per cent.

Water (2.3.43). Not more than 0.5 per cent, determined on 0.5 g.

Assay. Determine by liquid chromatography (2.4.14),

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

Test solution. Dissolve 30 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.

Reference solution. A 0.03 per cent w/v solution of *pretomanid IPRS* in the solvent mixture. *[NOTE- Sonicate to dissolve, if necessary]*

Use chromatographic system as described under Related substances, with the following modification.

- spectrophotometer set at 330 nm.

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 1.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{14}H_{12}F_3N_3O_5$.

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