Pretomanid Tablets

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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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Further follow-up action as required.	

Pretomanid Tablets

Pretomanid Tablets contain not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of pretomanid, $C_{14}H_{12}F_3N_3O_5$.

Usual strength. 200 mg.

Identification

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 (a).

Tests

Dissolution (2.5.2).

Apparatus No. 2 (Paddle),
Medium. 1000 ml of 0.5 per cent w/v solution of *hexadecyltrimethylammonium bromide* in *0.1 M hydrochloric acid*,
Speed and time. 75 rpm and 30 minutes.

Withdraw a suitable volume of the medium and filter. Measure the absorbance of the filtered solution, suitably diluted with the medium, if necessary, at the maximum at about 335 nm (2.4.7), using 1 cm quartz cell. Calculate the content of $C_{14}H_{12}F_3N_3O_5$ in the medium from the absorbance obtained from a solution of known concentration of *pretomanid IPRS* in dissolution medium.

Q. Not less than 75 per cent of the stated amount of $C_{14}H_{12}F_3N_3O_5$.

Related substances. Determine by liquid chromatography (2.4.14).

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

Test solution. Disperse a quantity of the powdered tablets containing 0.2 g of Pretomanid in solvent mixture with the aid of ultrasound for 45 minutes with intermittent shaking and dilute to 200.0 ml with the solvent mixture, Centrifuge a portion of the solution at 5000 rpm for 10 minutes. Use the supernatant liquid.

Reference solution (a). A 0.0005 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 15 cm × 4.6 mm, packed with octadecylsilane bonded to porous silica (3.5 µm), (such as Zorbax SB-C18),
- column temperature: 35°,
- mobile phase: A. dissolve 1.36 g of *potassium dihydrogen orthophosphate* in 1000 ml of *water*, adjusted to pH 2.0 with *dilute orthophosphoric acid*,
  B. *acetonitrile*,
- a gradient programme using the conditions given below,
- flow rate: 1 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	65	35
16	60	40
18	53	47
21	75	25
23	85	15

28	30	70
38	30	70
40	65	35
45	65	35

Name	Relative retention time
Pretomanid dimer impurity[1*]	0.64
Methoxy impurity[2*]	0.70
Benzyloxy Propanol impurity[3*]	0.92
Ortho isomer imputrity[4*]	0.87
Meta isomer impurity[5*]	0.95
Pretomanid	1.0
Benzyloxy propyl pivalate impurity[6*]	2.07

*Process impurity included for identification only. Not to be calculated and included in total degradation product.
[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](2S)-3-(2-bromo-4-nitro-1*H*-imidazol-1-yl)-2-{[4-(trifluoromethoxy) benzyl] oxy} propan-1–ol,
[4] (6S)-2-nitro-6-{[2-(trifluoromethoxy)benzyl]oxy}-6,7-dihydro-5*H*-imidazo[2,l-b]1,3}oxazine,
[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 1.4 in the chromatogram obtained with reference solution (b), the column efficiency is not less than 22000 theoretical plates, the tailing factor is not more than 2.0 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 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 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 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Microbial contamination (2.2.9). Total aerobic viable count is not more than 10^3 CFU per g and the total combined yeasts and molds count is not more than10^2 CFU per g. 1 g is free from *Escherichia coli*.

Uniformity of dosage units (2.5.4). Complies with the test stated under Uniformity of dosage units.

Other tests. Comply with the tests stated under Tablets.

Assay. Determine by liquid chromatography (2.4.14),

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

Test solution. Weigh and powder 20 tablets. Disperse a quantity of the powdered tablets containing 0.2 g of Pretomanid in the solvent mixture with the aid of ultrasound for 30 minutes with intermittent shaking and dilute to 200.0 ml with the solvent mixture. Centrifuge a portion of the solution at 5000 rpm for 10 minutes. Dilute 4.0 ml of supernatant liquid to 25.0 ml with the solvent mixture.

Reference solution (a). A 0.016 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]*

Use chromatographic system as described under Related substances.

Inject reference solution (a) and (b). The test is not valid unless The test is not valid unless the resolution between the peaks due to meta isomer impurity and pretomanid is not less than 1.4 in the chromatogram obtained with reference solution (b), the column efficiency is not less than 22000 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 in the chromatogram obtained with reference solution (a).

Inject reference solution (a) and the test solution.

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

Storage. Store at temperature not exceeding 30º.

hexadecyltrimethylammonium bromide (Cetyltrimethylammonium Bromide)