Delamanid

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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 lab.ipc@gov.in, with a copy to Dr. Gaurav Pratap Singh (email: gpsingh.ipc@gov.in) before the last date for comments.

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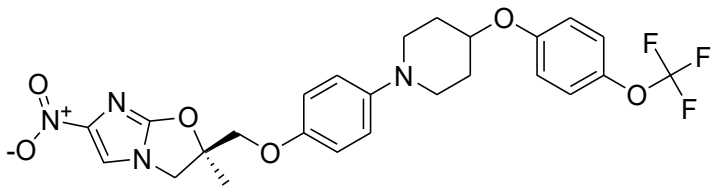
Delamanid



$C_{25}H_{25}F_3N_4O_6$ Mol. Wt. 534.5

Delamanid is (R)-2-methyl-6-nitro-2-[(4-{4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}phenoxy)methyl]-2,3-dihydroimidazo[2,1-b]oxazole.

Delamanid contains not less than 98.5 per cent and not more than 101.5 per cent of $C_{25}H_{25}F_3N_4O_6$, calculated on the dried basis.

Category. Antitubercular.

Description. A White to pale yellow crystals or crystalline powder.

Identification

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

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).

NOTE — Protect the solutions from light.

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 *delamanid –s-isomer IPRS* in *methanol*.

Reference solution (b). Dilute 1.0 ml of reference solution (a) to 20.0 ml with *methanol*. Dilute 1.0 ml of the solution to 10.0 ml with *methanol.*

Reference solution (c). Dissolve 6.25 mg of *delamanid–s–isomer IPRS* in *methanol* and dilute to 10.0 ml with *methanol*. Transfer 2.0 ml of the solution to a 100-ml volumetric flask, add 5.0 ml test solution and dilute to volume with *methanol*.

Reference solution (d). Dilute 2.0 ml of reference solution (b) to 20.0 ml with *methanol*.
Chromatographic system
- a stainless steel column 25 cm × 4.6 mm, packed with amylose tris-(3,5-dimethylphenylcarbamate) bonded to spherical silica (5 µm) (such as Chiral PAK AD-H),
- column temperature: 25°,
- mobile phase: a mixture of 70 volumes of *ethanol,* 30 volumes of *n-hexane* and 0.1 volumes of *diethylamine*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 245 nm,
- injection volume: 10 µl.

Name	Relative retention time
Delamanid	1.0
Delamanid-s-isomer[1]	1.45

[1](2*S*)-2-methyl-6-nitro-2-[(4-{4-[4-(trifluoromethoxy)phenoxy)piperidin-1-yl}phenoxy)methyl]-2,3-dihydroimidazo[2,1-*b*]oxazole.

Inject reference solution (b), (c) and (d). The test is not valid unless the resolution between the peaks due to delamanid and enantiomer of delamanid (delamanid-s-isomer) is not less than 5.0 in the chromatogram obtained with reference solution (c) and the relative standard deviation for replicate injections is not more than 2.0 per cent in the chromatogram obtained with reference solution (b) and the area of the principal peak in the chromatogram obtained with the reference solution (d) is between 7 per cent to 13 per cent of that 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 delamanid-s-isomer is not more than 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent).

Benzene. Determine by gas chromatography (2.4.13).

Test solution. Weigh and transfer 0.2 g of the substance under examination into a 20 ml-headspace vial, add 2.0 ml of *N,N-dimethylacetamide* and 5.0 ml of *water*, seal the vial immediately.

Reference solution. Weigh and transfer 0.2 g of *benzene* to a 100-ml volumetric flask containing 15 ml of *N,N-dimethylacetamide* and dilute to volume with *N,N-dimethylacetamide*. Dilute 1.0 ml of the solution to 100.0 ml with *N,N-dimethylacetamide*. Further dilute 1.0 ml of this solution to 100.0 ml with *N,N-dimethylacetamide*. Transfer 2.0 ml of the solution into a 20 ml-headspace vial, add 5.0 ml of *water* and seal the vial immediately.

Chromatographic system
– a fused silica column 60 m × 0.25 mm, packed with 100 per cent dimethylpolysiloxane (film thickness 1 µm) (such as DB-1),
– temperature:
column. 40° for 0 minutes, 40° to 100° @ 4° per minute, 100° to 250° @ 30° per minute and hold at 250° for 15 minutes,
– flame ionization detector,
– split ratio: 10:1,
– flow rate: 1.7 ml per minute, using helium as carrier gas,
– injection volume: 1 ml.

Head-space conditions
– vial temperature: 80°,
– loop temperature: 110°,
– transfer-line temperature: 120°,
– GC cycle time: 45 minutes,
– vial equilibration time: 30 minutes,
– vial pressurization time: 0.20 minutes,
– loop fill time: 0.1 minutes,
– loop equilibration time: 0.02 minutes,
– injection time: 1 minute,
– vial pressure: 14 psi.

Inject the reference solution. The test is not valid unless the column efficiency is not less than 200000 theoretical plates 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 benzene is not more than the area of the principal peak in the chromatogram obtained with the reference solution (2 ppm).

2-Bromo-4-nitroimidazole. Determine by liquid chromatography (2.4.14).

NOTE — Protect the solutions from light.

Test solution. Weigh and transfer 1 g of the substance under examination to a 50-ml volumetric flask, add 10.0 ml of *tetrahydrofuran* and 20.0 ml of *water*, shake well and filter off the precipitated crystal, filter the filtrate through 0.45 µm PTFE filter, discard the initial 2 ml of filtrate and use the subsequent filtrate as the sample solution *[Note – If the substance is difficult to dissolve, warm it up]*.

Reference solution. A 0.00015 per cent w/v solution of *2-bromo-4-nitroimidazole IPRS* in *tetrahydrofuran*. Transfer 2.0 ml of the solution to a 50-ml volumetric flask, add 8.0 ml of *tetrahydrofuran* and add 20.0 ml of *water*, mix.

Chromatographic system
- a stainless steel column 25 cm × 4.6 mm, packed with octylsilane bonded to porous silica (5 µm) (such as YMC-Pack Pro C8),
- column temperature: 25°,
- mobile phase: A. a mixture of 85 volumes of *water*, 15 volumes of *acetonitrile* and 0.2 volumes of *acetic acid*,
  B. a mixture of 80 volumes of *methanol* and 20 volumes of *acetonitrile*,
- a gradient programme using the conditions given below,
- flow rate: 1 ml per minute,
- spectrophotometer set at 305 nm,
- injection volume: 50 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	100	0
12	100	0
13	50	50
15	20	80
17	0	100
30	0	100
32	100	0
52	100	0

Inject the reference solution. The test is not valid unless the column efficiency is not less than 10000 theoretical plates 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 2-bromo-4-nitroimidazole is not more than the area of the principal peak in the chromatogram obtained with the reference solution (3 ppm).

Tert-Butyl acetate. Determine by gas chromatography (2.4.13).

Test solution. Weigh and transfer 0.5 g of the substance under examination into a 20 ml-headspace vial, add 5.0 ml of *1,3-dimethyl-2-imidazolidinone* and seal the vial immediately.

Reference solution. Weigh and transfer 50 mg of *tert-butyl acetate* to a 100-ml volumetric flask containing 20 ml of *1,3-dimethyl-2- imidazolidinone* and dilute to volume with *1,3-dimethyl-2- imidazolidinone*. Dilute 5.0 ml of the solution to 50.0 ml with *1,3-dimethyl-2- imidazolidinone*. Transfer 5.0 ml of this solution into a 20 ml-headspace vial and seal the vial immediately.

Chromatographic system
- a capillary column 60 m × 0.32 mm, packed with 6.0 per cent cyanopropyl and 94 per cent dimethylpolysiloxane (film thickness 1.8 µm) (such as DB-624),
- temperature:

column. 40° for 4 minutes, 40° to 160° @ 15° per minute and hold at 160° for 3 minutes, 160° to 240° @ 50° per minute and hold at 240° for 5 minutes,
inlet port at 200° and detector at 250°,
– flame ionization detector,
– split ratio: 1:10,
– flow rate: 3.5 ml per minute, using helium as carrier gas,
– injection volume: 1 ml.

Head-space conditions
– vial temperature: 120°,
– loop temperature: 125°,
– transfer-line temperature: 130°,
– GC cycle time: 35 minutes,
– vial equilibration time: 15 minutes,
– vial pressurization time: 0.20 minutes
– loop fill time: 0.1 minutes,
– loop equilibration time: 0.05 minutes,
– injection time: 1 minute,
– vial pressure: 14 psi.

Name	Relative retention time
tert-Butyl acetate	0.56
1,3-Dimethyl-2- imidazolidinone	1.0

Inject the reference solution. The test is not valid unless 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 tert-butyl acetate is not more than the area of the principal peak in the chromatogram obtained with the reference solution (500 ppm).

Related substances. A. Determine by liquid chromatography (2.4.14).

NOTE — Protect the solutions from light.

Solvent mixture. 80 volumes of *acetonitrile* and 20 volumes of *water*.

Test solution. Dissolve 50 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). A 0.00025 per cent w/v solution of *delamanid IPRS* in the solvent mixture.

Reference solution (b). Dilute 2.0 ml of reference solution (a) to 20.0 ml with the solvent mixture.

Chromatographic system
– a stainless steel column 25 cm × 4.6 mm, packed with octylsilane bonded to porous silica (5 µm), (such as TSK gel Octyl-80Ts),
– column temperature: 40°,
– mobile phase: a mixture of 65 volumes of a buffer solution prepared by dissolving 6.3 g of *ammonium formate* in 1000 ml of *water* and 35 volumes of *methanol*,
– flow rate: 1 ml per minute,
– spectrophotometer set at 238 nm,
– injection volume: 10 µl.

Name	Relative retention time	Correction factor

Des TFM delamanid[1]	0.47	0.90
Dihydrooxazolamine impurity[2]	0.58	1.35
HTP propanol urea impurity[3]	0.75	1.15
Delamanid	1.0	---
3-TFM delamanid[4]	1.09	1.05
Methoxy analog of bromo intermediate[5]	1.44	1.11
Bromo intermediate[6]	1.55	---
R-ETP[7]	1.9	1.10

[1](2*R*)-2-methyl-6-nitro-2-((4-(4-(phenoxypiperidin-1-yl)phenoxy)methyl)-2,3-dihydroimidazo[2,1-b]oxazole,
[2](5*R*)-5-methyl-5-((4-(4-(4-(trifluoromethoxy)phenoxy)piperidin-1-yl)phenoxy)methyl)-4,5-dihydrooxazol-2-amine,
[3](2*R*)-1-(2-hydroxy-2-methyl-3-(4-(4-(4-(trifluoromethoxy) phenoxy)piperidin-1-yl)phenoxy)propyl)urea,
[4](2*R*)-2-methyl-6-nitro-2-((4-(4-(3-(trifluoromethoxy)phenoxy)piperidin-1-yl)phenoxy)methyl)-2,3-dihydroimidazo[2,1-b]oxazole,
[5](2*R*)-1-(2-methyoxy-4-nitro-1H-imidazol-1-yl)-2-methyl-3-(4-(4-(4-(trifluoromethoxy)phenoxy)piperidin-1-yl)phenoxy)propan-2-ol,
[6](2*R*)-1-(2-bromo-4-nitro-1H-imidazol-1-yl)-2-methyl-3-(4-(4-(4-(trifluoromethoxy)phenoxy)piperidin-1-yl)phenoxy)propan-2-ol,
[7](2*R*)-1-{4-[(2-methyloxiran-2-yl)methoxy]phenyl}-4-[4-(trifluoromethoxy)phenoxy]-piperidine.

Inject reference solution (a) and (b). The test is not valid unless the column efficiency is not less than 12000 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 in the chromatogram obtained with the reference solution (a) and the area of the principal peak in the chromatogram obtained with the reference solution (b) is between 7 per cent to 13 per cent of that obtained in the chromatogram with the 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 des TFM delamanid, dihydrooxazolamine impurity, HTP propanol urea impurity, 3-TFM delamanid, methoxy analog of bromo intermediate, bromo intermediate and R-ETP, each of, 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 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).

B. Determine by liquid chromatography (2.4.14) as described in Related substances A with the following modifications.

Chromatographic system
- a stainless steel column 15 cm × 4.6 mm, packed with octylsilane bonded to porous silica (5 µm), (such as TSK gel Octyl-80Ts),
- column temperature: 40°,
- mobile phase: a mixture of 20 volumes of a buffer solution prepared by dissolving 6.3 g of *ammonium formate* in 1000 ml of *water* and 80 volumes of *methanol*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 238 nm,
- injection volume: 10 µl.

Name	Relative retention time	Correction factor
Delamanid	1.0	---
HTP delamanid impurity[1]	3.05	1.03
Bis HTP methyl propanol impurity[2]	4.5	1.01

[1](2*R*)-2-methyl-6-nitro-2-((4-(4-(4-(trifluoromethoxy)phenoxy)piperidin-1-yl)-2-(4-(4-(4-(trifluoromethoxy)phenoxy)piperidin-1-yl)phenoxy)phenoxy)methyl)-2,3-dihydroimidazo[2,1-b]oxazole,
[2]2-methyl-1,3-bis(4-(4-(4-(trifluoromethoxy)phenoxy)piperidin-1-yl)phenoxy)propan-2-ol.

Inject reference solution (a) and (b). The test is not valid unless the column efficiency is not less than 3000 theoretical plates and the relative standard deviation for replicate injections is not more than 2.0 per cent in the chromatogram obtained with the reference solution (a) and the area of the principal peak in the chromatogram obtained with the reference solution (b) is between 7 per cent to 13 per cent of that 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 HTP delamanid impurity and bis HTP methyl propanol impurity, each of, 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).

The sum of the impurities (from Related substances A and B) is not more than 0.2 per cent.

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

Loss on drying (2.4.19). Not more than 0.5 per cent, determined on 1.0 g by drying in an oven at 105° for 3 hours.

Assay. Determine by liquid chromatography (2.4.14),

NOTE — Protect the solutions from light.

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

Internal standard solution. A 1 per cent w/v solution of *isoamyl 4-hydroxybenzoate* in *acetonitrile*.

Test solution. Dissolve 0.1 g of the substance under examination in *acetonitrile* with the aid of ultrasound, add 10.0 ml of the internal standard solution and dilute to 100.0 ml with the *acetonitrile*. Dilute 5.0 ml of the solution to 50.0 ml with the solvent mixture.

Reference solution. Dissolve 0.1 g of *delamanid IPRS*, in *acetonitrile* with the aid of ultrasound, add 10.0 ml of the internal standard solution and dilute to 100.0 ml with the *acetonitrile*. Dilute 5.0 ml of the solution to 50.0 ml with the solvent mixture.

Chromatographic system
- a stainless steel column 10 cm × 4.6 mm, packed with octylsilane bonded to porous silica (3 µm), (such as Sunniest C8),
- column temperature: 40°,
- mobile phase: a mixture of 35 volumes of a buffer solution prepared by dissolving 0.63 g of *ammonium formate* in 1000 ml of *water* and 65 volumes of *methanol*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 238 nm,
- injection volume: 10 µl.

Inject the reference solution. The test is not valid unless the resolution between the peaks due to isoamyl 4-hydroxybenzoate (internal standard) and delamanid is not less than 10.0 and the relative standard deviation of the ratio of peak area of delamanid to that of peak area of the internal standard, for replicate injections is not more than 1.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{25}H_{25}F_3N_4O_6$ using ratio of the peak area of delamanid to that of peak area of the internal standard.

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