

Draft Proposal for Comments and Inclusion in The Indian Pharmacopoeia

Velpatasvir

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This draft proposal contains monograph text for inclusion in the Indian Pharmacopoeia (IP). The content of this draft document is not final, and the text may be subject to revisions before publication in the IP. This draft does not necessarily represent the decisions or the stated policy of the IP or Indian Pharmacopoeia Commission (IPC).

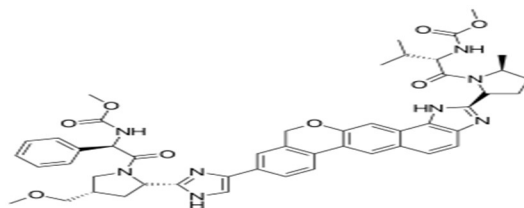
Manufacturers, regulatory authorities, health authorities, researchers, and other stakeholders are invited to provide their feedback and comments on this draft proposal. Manufacturers are also invited to submit samples of their products to the IPC to ensure that the proposed monograph adequately controls 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

Description	Details
Document version	1.0
Monograph proposed for inclusion	IP Addendum 2024
Tentative effective date of monograph	April, 2024
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Draft revision published on IPC website for public comments	-
Further follow-up action as required.	

Velpatasvir



C₄₉H₅₄N₈O₈

Mol. Wt. 883.0

Velpatasvir is methyl {(1*R*)-2-[(2*S*,4*S*)-2-(5-{2-[(2*S*,5*S*)-1-{(2*S*)-2-(methoxycarbonyl)amino]-3-methyl butanoyl}-5-methylpyrrolidin-2-yl]-1,1-dihydroisochromeno[4',3':6,7] naphthol [1,2-*d*]imidazol-9-yl]-1*H*-imidazol-2-yl]-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl]carbamate.

Velpatasvir contains not less than 97.0 per cent and not more than 103.0 per cent of Velpatasvir, C₄₉H₅₄N₈O₈, calculated on the anhydrous basis.

Category. Antiviral for treatment of HCV infections.

Description. A white to yellow or tan or pink colour powder.

Identification

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

B. In the Assay, the principal peak in the chromatogram obtained with test solution corresponds to the principal peak in the chromatogram obtained with the reference solution.

Tests

Related substances. Determine by liquid chromatography (2.4.14).

NOTE — Since the material is hygroscopic in nature, it is appropriate to weigh the samples under dehumidified area (35 ± 5 % RH).

Solvent mixture. 30 volumes of acetonitrile and 70 volumes of water.

Test solution. Dissolve 25 mg of the substance under examination in 30.0 ml acetonitrile and dilute to 100.0 ml with water.

Reference solution (a). Dissolve 25 mg of *velpatasvir* IPRS in 30 ml of acetonitrile and dilute to 100.0 ml with water. Dilute 5.0 ml of the solution to 100.0 ml with the solvent mixture. Further dilute 2.0 ml of the solution to 100.0 ml with the solvent mixture.

Reference solution (b) A solution containing 0.25 per cent w/v of *velpatasvir* IPRS and 0.000375 per cent w/v, each of *velpatasvir* impurity A IPRS, *velpatasvir* impurity B IPRS, *velpatasvir* impurity C IPRS, *velpatasvir* impurity D IPRS, *velpatasvir* impurity E IPRS, *velpatasvir* impurity G IPRS in acetonitrile. Dilute 1.0 ml of the solution to 10.0 ml with the solvent mixture.

Reference solution (c). Dissolve 2.5 mg of *velpatasvir* impurity F IPRS (lactone impurity) in 30 ml of acetonitrile and dilute to 100.0 ml with the solvent mixture. Dilute 1.0 ml of the solution to 20.0 ml with the solvent mixture.

Chromatographic system

- a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (3.5 μm) (Such as X Select CSH C 18),

- Column temperature: 45^o,
- sample temperature: 10^o,
- mobile phase: A. a buffer solution prepared by dissolving 1.15 g of *ammonium dihydrogen phosphate* in 1000 ml of *water* and, adjusted to pH 2.0 with 20 per cent v/v of *trifluoroacetic acid* in *water*,
B. *acetonitrile*,
- flow rate: 1 ml per minute,
- a gradient programme using the conditions given below,
- spectrophotometer set at 295 nm,
- injection volume: 20 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	75	25
20	70	30
25	65	35
30	30	70
35	30	70
36	75	25
40	75	25

Name	Relative retention time	Correction factor
Impurity at RRT of about 0.29 ¹	0.29	----
Impurity at RRT of about 0.34 ¹	0.34	----
Velpatasvir Impurity A ²	0.35	----
Impurity at RRT of about 0.41 ¹	0.41	----
Impurity at RRT of about 0.53 ¹	0.53	----
Impurity at RRT of about 0.68 ¹	0.68	----
Velpatasvir Impurity B ³	0.70	----
Velpatasvir Impurity C ⁴	0.77	3.23
Velpatasvir Impurity D ⁵	0.89	----
Impurity at RRT of about 0.90 ¹	0.90	----
Impurity at RRT of about 0.95 ¹	0.95	----
Velpatasvir (Retention time: about 19 minutes)	1.0	----
Velpatasvir Impurity E ⁶	1.07	1.35
Velpatasvir Impurity F ⁷	1.17	----
Impurity at RRT of about 1.22 ¹	1.22	----
Velpatasvir Impurity G ⁸	1.35	1.39
Impurity at RRT of about 1.42 ¹	1.42	----
Impurity at RRT of about 1.48 ¹	1.48	----

Note-(1) The peaks due to Impurity at RRT of about 0.34 and velpatasvir impurity A, Impurity at RRT of about 0.68 and Velpatasvir Impurity B and Velpatasvir Impurity D, Impurity at RRT of about 0.90 may coelute or single peak, make base to base integration if the both peaks are separated and report the results using the sum of the areas of both the peaks.

(2) The peaks of impurity at RRT of about 0.53 is in broad shape.

¹unknown structure.

²methyl {(2S)-1-[(2S,5S)-2-(9-{2-[(2S,4S)-4-(methoxymethyl)pyrrolidine-2-yl]-1H-imidazol-5-yl})-1,11-dihydroisochromeno[4',3':6',7']naphthol[1,2-d]imidazole-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl} carbamate. (amine free base)

³methyl {(2S)-1-[(2S,5S)-2-(9-[2-[(2S,4S)-1-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-(methoxymethyl)pyrrolidin-2-yl]-1H-imidazol-5yl]-1,11-dihydroisochromeno[4',3':6',7'] naphthol[1,2-d]imidazole-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl} carbamate. (CDMT impurity)

⁴methyl {(1R)-2-[(2S,4S)-2-(5-[2-[(2S,5S)-1-(2S)-2[(methoxycarbonyl)amino]-3-methylbutanoyl]-5-methylpyrrolidin-2-yl]-1,4,5,11-tetrahydroisochromeno[4',3':6',7'] naphthol[1,2-d]imidazole-9-yl)-1H-imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl} carbamate. (Diimidazole impurity)

⁵methyl {1S)-2-[(2S,4S)-2-(5-[2-[(2S,5S)-1-[(2S)-2[(methoxycarbonyl)amino]-3-methylbutanoyl]-5-methylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6',7'] naphthol[1,2-d]imidazol-9-yl)-1H-imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl} carbamate. (S-Moc phenyl glycine isomers)

⁶methyl {(1R)-2-[(2S,4S)-2-(5-[2-[(2S,4S)-1-[(2R)-2[(methoxycarbonyl)amino]-2-phenylacetyl]-4-(methoxymethyl)pyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6',7'] naphthol[1,2-d]imidazole-9-yl)-1H-imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl} carbamate. (Intermediate-I Dimer impurity)

⁷methyl {(1R)-2-[(2S,4S)-2-(5-[2-[(2S,5S)-1-[(2S)-2[(methoxycarbonyl)amino]-3-methylbutanoyl]-5-methylpyrrolidin-2-yl]-1-oxo-1,11-dihydroisochromeno[4',3':6',7'] naphthol[1,2-d]imidazole-9-yl)-1H-imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl]carbamate. (Lactone impurity)

⁸methyl {(1R)-2-[(1R)-2-[(2S,4S)-2-(5-[5-2-[(2S,5S)-1-[(2S)-2[(methoxycarbonyl) amino]-3-methylbutanoyl]-5-methylpyrrolidin-2-yl]-1,11-dihydroisochromeno[4',3':6',7'] naphthol[1,2-d]imidazole-9-yl)-1H-imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl]amino)-2-oxo-1-phenylethyl]carbamate. (Glycine dimer impurity)

Inject reference solutions (b) and (c) to identify the peaks due to velpatasvir impurity A, B, C, D, E, G, and F respectively.

Inject reference solution (a) and (b). The test is not valid unless the resolution between the peaks due to velpatasvir and Velpatasvir Impurity E is not less than 2.5 and between Velpatasvir Impurity E and Velpatasvir Impurity F is not less than 1.2 in the chromatogram obtained with reference solution (b) and 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 peak corresponding to the impurity at RRT of about 0.29, impurity at RRT of about 0.34, Velpatasvir impurity A, impurity at RRT of about 0.41, impurity at RRT of about 0.53, impurity at RRT of about 0.68, Velpatasvir impurity B, Velpatasvir impurity C, Velpatasvir impurity D, impurity at RRT of about 0.90, impurity at RRT of about 0.95, Velpatasvir impurity E, Velpatasvir impurity F, impurity at RRT of about 1.22, Velpatasvir impurity G, impurity at RRT of about 1.42 and impurity at RRT of about 1.48, each of, is not more than 5 times the area of the velpatasvir peak in the chromatogram obtained with reference solution (a) (0.5 per cent), the area of any other secondary peak is not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent), and the sum of areas of all the secondary peak is not more than 10 times the area of principal peak with the 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).

Heavy metals (2.3.13). 1.0 g complies with the limit test for heavy metals, Method B (20 ppm).

Sulphated ash (2.3.18). Not more than 0.1 per cent, determined on 1.0 g, using platinum crucible.

Water (2.3.43). Not more than 6.0 per cent.

Assay. Determine by liquid chromatography (2.4.14).

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

Test solution. Dissolve 50 mg of the substance under examination in 60 ml of the *acetonitrile* and dilute to 100.0 ml with *water*. Dilute 1.0 ml of the solution to 10.0 ml with the *solvent mixture*.

Reference solution. Dissolve 50 mg of *velpatasvir IPRS* in 60 ml of *acetonitrile* and dilute to 100.0 ml with *water*. Dilute 1.0 ml of the solution to 10.0 ml with the *solvent mixture*.

Chromatographic system

- a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (3.5 µm) (Such as Symmetry C18),
- Column temperature: 45^o,
- mobile phase: A. 0.1 per cent v/v of *trifluoroacetic acid* in *water*.
B. *acetonitrile*,
- a gradient programme using the conditions given below,
- flow rate: 1 ml per minute,
- spectrophotometer set at 300 nm,
- injection volume: 20 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	75	25
5	70	30
15	70	30
20	60	40

21
2575
7525
25

Inject the reference solution. The test is not valid unless the column efficiency is not less than 10000 theoretical plates, the tailing factor is not more than 1.8 and the relative standard deviation of replicate injections is not more than 1.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of velpatasvir, $C_{49}H_{54}N_8O_8$.

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

Solubility (2.4.26). Soluble in *methanol* and *dichloromethane*.

Draft for Comments