Velpatasvir

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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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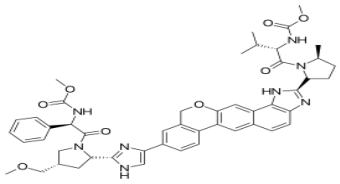
Velpatasvir



$C_{49}H_{54}N_8O_8$ 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]-1,11-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.

Velpatasvir contains not less than 97.0 per cent and not more than 103.0 per cent of velpatasvir, $C_{49}H_{54}N_8O_8$, calculated on the anhydrous basis.

Category. Anti-retroviral

Description. A white to tan or yellow 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 the test solution corresponds to the peak in the chromatogram obtained with the reference solution.

Tests

Related substances. Determine by liquid chromatography (2.4.14).

NOTE- The material is hygroscopic in nature.

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

Test solution. Dissolve 25 mg of the substance under examination in 30 ml of *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 1.0 ml of the solution to 100.0 ml with the solvent mixture. Dilute 1.0 ml of the solution to 10.0 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 C18),
- column temperature: 45°,
- sample temperature: 10°,
- mobile phase: A. a buffer solution prepared by dissolving 1.15 g of *ammonium dihydrogen phosphate* in 1000 ml of *water*, adjusted to pH 2.0 with 20 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 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.

[1]unknown structure.

[2]methyl {(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-methylprrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate. (amine free base)

[3]methyl {(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)

[4]methyl {(1R)-2-[(2S,4S]-2-(5-[2-[(2S,5S)-1-[(2S)-2[(methoxycarbonyl)amino]-3-methylbutanoyl]-5-methylpyrrolidin-2-yl]-1,4,5,11-tetrahydro isochromeno[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)

[5]methyl {1S)-2-[(2S,4S)-2-(5-{2-[(2S,5S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoly}-5methylpyrrolidin-2-yl}-1,11-dihydroiso chromeno[4’,3’:6’,7’}naphtho[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)

[6]methyl {(1R)-2-[(2S,4S]-2-(5-[2-[(2S,4S)-1-[(2R)-2[(methoxycarbonyl)amino]-2-phenylacetyl}-4-(methoxymethyl)pyrrolidin-2-yl]-1,11-dihydro isochromeno[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)

[7]methyl {(1R)-2-[(2S,4S]-2-(5-[2-[(2S,5S)-1-[(2S)-2[(methoxycarbonyl)amino]-3-methylbutanoyl]-5-methylpyrrolidin-2-yl]-11-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)

[8]methyl {(1R)-2-({(1R)-2-[(2S,4S)-2-(5-{5-2-[(2S,5S)-1-{(2S)-2[(methoxycarbonyl) amino]-3-methylbutanoyl}-5-methylpyrrolidin-2yl}-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 solution (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 the principal peak 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).

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, using platinum crucible.

Water (2.3.43). Not more than 6.0 per cent, determined on 0.5 g.

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 *acetonitrile* and dilute to100.0 ml with *water*. Dilute 1.0 ml of the solution to 10.0 ml with the solvent mixture.

Reference solution. Dissolve 25 mg of *velpatasvir IPRS* in 30 ml of *acetonitrile* and dilute to 50.0 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°,
- mobile phase: A. 0.1 per cent v/v solution 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	75	25
25	75	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 for replicate injections is not more than 1.0 per cent.

Inject the reference solution and the test solution.

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

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

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