Daclatasvir 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. 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

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Further follow-up action as required.	

Daclatasvir Tablets

Daclatasvir Dihydrochloride Tables

Daclatasvir Tablets contain daclatasvir dihydrochloride equivalent to not less than 95.0 per cent and not more than 105.0 per cent of the stated amount of daclatasvir, $C_{40}H_{50}N_8O_6$.

Usual strengths. 30 mg; 60 mg.

Identification

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

B. Disperse a quantity of the powdered tablets containing 120 mg of daclatasvir in *methanol* with the aid of ultrasound for 60 minutes with intermittent shaking and dilute to 100.0 ml with *methanol*. Centrifuge a portion of the solution at 5000 rpm for 10 minutes. Dilute 3.0 ml of clear supernatant liquid to 250.0 ml with a mixture of equal volumes of *methanol* and *water*, filter. When examined in the range 200 nm to 360 nm (2.4.7), the resulting solution shows an absorption maximum between 312 nm and 316 nm.

Tests

Dissolution (2.5.2).

Apparatus No. 2 (Paddle),
Medium:1000 ml of *phosphate buffer pH 6.8* with 0.75 per cent *Brij 35*, prepared by dissolving 6.8 g of *potassium dihydrogen orthophosphate* and 1.8 g of *sodium hydroxide* in 1000 ml of *water*, adjusted to pH 6.8 with *0.2 M sodium hydroxide*, add 7.5 g of *Brij 35*, mix,
Speed and time: 75 rpm and 30 minutes,

Withdraw a suitable volume of the medium and filter.

Determine by liquid chromatography (2.4.14).

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

Test solution. Use the filtrate, dilute if necessary, with the dissolution medium.

Reference solution. Dissolve 66 mg of *daclatasvir dihydrochloride IPRS* in *methanol* with the aid of ultrasound for 5 minutes and dilute to 50.0 ml with *methanol*. Dilute a suitable volume with the solvent mixture to obtain a solution having a known concentration similar to the test solution.

Chromatographic system
- a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (Such as Inertsil ODS-3V),
- column temperature: 35°,
- sample temperature:10°,
- mobile phase: A. a buffer solution prepared by dissolving 1.36 g of *potassium dihydrogen orthophosphate* in 900 ml of *water*, add 2 ml of *triethylamine*, mix and dilute to 1000 ml with *water*, adjusted to pH 2.5 with *dilute orthophosphoric acid*
  B. *acetonitrile*,
- a gradient programme using the conditions given below,
- flow rate: 1.3 ml per minute,
- spectrophotometer set at 318 nm,
- injection volume: 10 µl,

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	75	25
2.5	45	55
4	75	25

6	75	25

Inject the reference solution. The test is not valid unless 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.

Inject the reference solution and the test solution.

Calculate the content of $C_{40}H_{50}N_8O_6$ in the medium.

Q. Not less than 80 per cent of the stated amount of $C_{40}H_{50}N_8O_6$.

Related substances. Determine by liquid chromatography (2.4.14).

NOTE— Prepare solutions immediately before use.

Test solution. Disperse a quantity of the powder containing 60 mg of Daclatasvir in *methanol* with the aid of ultrasound for 30 minutes with intermittent shaking and dilute to 100.0 ml with *methanol*. Centrifuge a portion of the solution at 5000 rpm for 10 minutes. Use the supernatant liquid.

Reference solution. A solution of *daclatasvir dihydrochloride IPRS* containing 0.0003 per cent w/v of daclatasvir in *methanol.*

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with octylsilane bonded to porous silica (5 µm) (Such as Zorbax-RX C8),
- column temperature: 35°,
- sample temperature: 10°,
- mobile phase: A. a mixture of 95 volumes of buffer solution prepared by dissolving 1.36 g of *potassium dihydrogen orthophosphate* in 900 ml of *water*, add 5 ml of *triethylamine* and 10 ml of *formic acid* mix and dilute to 1000 ml with *water*, adjusted to pH 2.5 with *formic acid* and 5 volumes of *acetonitrile,*

  B. a mixture of 40 volumes of *acetonitrile*, 50 volumes of *methanol* and 10 volumes of *water,*
- a gradient programme using the conditions given below,
- flow rate: 1.2 ml per minute,
- spectrophotometer set at 300 nm,
- injection volume: 10 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	70	30
25	65	35
35	50	50
40	20	80
50	20	80
55	70	30
60	70	30

Name	Relative retention time
Daclatasvir	1.0
LL, DL-Diastereomer of Daclatasvir*	1.4
N-Moc-L Isoleucine analogue impurity*	1.6
LL, DD-Diastereomer of Daclatasvir*	1.8

*Process impurity, included for identification only and not to be included in the calculation of total degradation product.

NOTE- The retention time, resolution and relative retention times of impurities are buffer pH sensitive.

Inject the reference solution. The test is not valid unless the tailing factor is not more than 2.0 and the relative standard deviation of 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 secondary peak is not more than the area of the principal peak in the chromatogram obtained with the reference solution

(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 the reference solution (2.0 per cent).

Uniformity of dosage units (2.5.4). Comply with the tests stated under Tablets.

Other tests. Comply with the tests stated under Tablets.

Assay. Determine by liquid chromatography (2.4.14).

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

Test solution. Weigh and powder 20 tablets. Disperse a quantity of the powder containing 90 mg of Daclatasvir in 6 ml of *water* with the aid of ultrasound, add 200 ml of *methanol.* Further sonicate for 60 minutes with intermittent shaking and dilute to 250.0 ml with *methanol*. Centrifuge a portion of solution at 5000 rpm for 10 minutes. Dilute 3.0 ml of the supernatant liquid to 20.0 ml with the solvent mixture.

Reference solution. A solution of *daclatasvir dihydrochloride IPRS* containing 0.108 per cent w/v of daclatasvir in *methanol*. Dilute 5.0 ml of the solution to 100.0 ml with the solvent mixture.

Chromatographic system

- a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (Such as Kromasil, 100-5 C18),
- column temperature: 30°,
- sample temperature:10°,
- mobile phase: a mixture of 60 volumes of buffer solution prepared by dissolving 1.36 g of *potassium dihydrogen orthophosphate* in 900 ml of *water*, add 1 ml of *triethylamine,* mix and dilute to 1000 ml with *water*, adjusted to pH 7.0 with *orthophosphoric acid* and 40 volumes of *acetonitrile,*
- flow rate: 1.5 ml per minute,
- spectrophotometer set at 318 nm,
- injection volume: 10 µl,

Inject the reference solution. The test is not valid unless 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.

Inject the reference solution and the test solution.

Calculate the content of $C_{40}H_{50}N_8O_6$ in the tablets.

Labelling. The label states the strength in terms of equivalent amount of daclatasvir.

1mg of daclatasvir dihydrochloride, $C_{40}H_{50}N_8O_6.2HCl$ is equivalent to 0.9102 mg of daclatasvir, $C_{40}H_{50}N_8O_6$.

Storage. Store at a temperature not exceeding 30°.