Dapagliflozin

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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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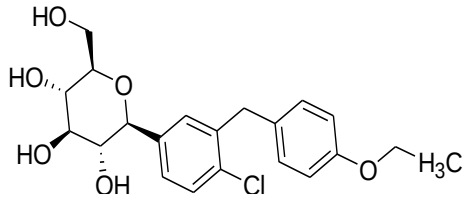
Dapagliflozin



$C_{21}H_{25}ClO_6$ Mol. Wt. 408.9

Dapagliflozin is (1S)-1,5-anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-D-glucitol.

Dapagliflozin contains not less than 98.0 per cent and not more than 102.0 per cent of $C_{21}H_{25}ClO_6$, calculated on the anhydrous basis.

Category. Antidiabetic.

Description. A white to off white powder or solid.

Identification

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

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

Specific optical rotation (2.4.22). +17.0° to +23.0°, determined in a 0.2 per cent w/v solution in *chloroform*.

Related substances. Determine by liquid chromatography (2.4.14).

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

Buffer solution. Dissolve 1.15 g of *ammonium dihydrogen orthophosphate* in 1000 ml of *water*, adjusted to pH 5.0 with *dilute ammonia solution*.

Test solution. Dissolve 40 mg of the substance under examination in the solvent mixture with the aid of ultrasound for 2 minutes and dilute to 50.0 ml with the solvent mixture.

Reference solution (a). A 0.0004 per cent w/v solution of *dapagliflozin IPRS* in the solvent mixture.

Reference solution (b). A solution containing 0.00012 per cent w/v, each of, *ortho isomer of dapagliflozin impurity IPRS* and *dapagliflozin dimer-1 impurity IPRS* and 0.08 per cent w/v of *dapagliflozin IPRS* in the solvent mixture.

Reference solution (c). Dilute 2.0 ml of reference solution (a) to 25.0 ml with the solvent mixture.

Chromatographic system
- a stainless steel column 10 cm × 4.6 mm, packed with octadecylsilane bonded to porous silica (2.6 µm) (Such as Kinetex XB-C 18),
- mobile phase: A. a mixture of 90 volumes of the buffer solution and 10 volumes of *acetonitrile*,
  B. a mixture of 20 volumes of the buffer solution and 80 volumes of *acetonitrile*,
- flow rate: 0.8 ml per minute,

– a gradient programme using the conditions given below,
– spectrophotometer set at 225 nm,
– injection volume: 10 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	80	20
50	10	90
75	10	90
77	80	20
85	80	20

Name	Relative retention time	Correction factor
Desethyl dapagliflozin[1]	0.37	1.10
Hydroxy dapagliflozin[2]	0.52	1.10
Oxo dapagliflozin[3]	0.73	1.17
Dapagliflozin	1.0	---
Ortho isomer of dapagliflozin[4]	1.06	1.10
Alpha isomer of dapagliflozin[5]	1.14	1.01
Dapagliflozin diamer-1[6]	1.58	0.95
Dapagliflozin dimer-2[7]	2.26	1.04
Acetyl dapagliflozin[8]	2.98	1.38

[1](2S,3R,4R,5S,6R)-2-(4-Chloro-3-(4-hydroxybenzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol.
[2](2S,3R,4R,5S,6R)-2-(4-Chloro-3-((4-ethoxyphenyl)(hydroxy)methyl)phenyl)-6-(hydroxymethyl) tetrahydro-2H-pyran-3,4,5-triol.
[3](2-Chloro-5-((2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)phenyl)(4-ethoxyphenyl)methanone.
[4](1S)-1,5-anhydro-1-C-{4-chloro-3-[(2-ethoxyphenyl)methyl]phenyl}-D-glucitol.
[5](1R)-1,5-anhydro-1-C-{4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl}-D-glucitol.
[6](2S,3R,4R,5S,6R)-2-[4-chloro-3-[(5-{2-Chloro-5-((2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl]benzyl]-2-ethoxyphenyl)(4-ethoxyphenyl)methyl]phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol.
[7](1S)-1,5-anhydro-1-C-{4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl}-6-O-[1-C-{4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl}D-glucopyranosyl]-D-glucitol.
[8](1S)-2,3,4,6-tetra-O-acetyl-1,5-anhydro-1-C-{4-chloro-3-[(4-ethoxyphenyl)methyl]-phenyl}-D-glucitol.

Inject reference solution (a), (b) and (c). The test is not valid unless the resolution between the peaks due to dapagliflozin and ortho isomer of dapagliflozin is not less than 3.0 in the chromatogram obtained with reference solution (b), the column efficiency is not less than 28000 theoretical plates, the tailing factor is not more than 1.5, the relative standard deviation of replicate injections is not more than 10.0 per cent in the chromatogram obtained with reference solution (a) and the signal to noise ratio is not less than 20 in the chromatogram obtained with reference solution (c).

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to desethyl dapagliflozin, hydroxy dapagliflozin, oxo dapagliflozin, ortho isomer of dapagliflozin, alpha isomer of dapagliflozin, dapagliflozin diamer-1, dapagliflozin dimer-2 and acetyl dapagliflozin, each of, is not more than 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent). 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) and the sum of the areas of all the secondary peaks is not more than 1.6 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.8 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).

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

Water (2.3.43). Not more than 0.3 per cent, determined on 0.2 g.

Assay. Determine by liquid chromatography (2.4.14),
Solvent mixture. Equal volumes of *acetonitrile* and *water*.

Test solution. Dissolve 50 mg of the substance under examination in the solvent mixture with the aid of ultrasound for 2 minutes and dilute to 100.0 ml with the solvent mixture. Dilute 5.0 ml of the solution to 50.0 ml with the solvent mixture.

Reference solution. A 0.005 per cent w/v solution of *dapagliflozin IPRS* in the solvent mixture.

Chromatographic system
- a stainless steel column 15 cm × 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (Such as Kromasil C18),
- mobile phase: a mixture of 55 volumes of a buffer solution prepared by dissolving 1.36 g of *potassium dihydrogen orthophosphate* in 1000 ml of *water*, adjusted to pH 2.0 with *orthophosphoric acid* and 45 volumes of *acetonitrile*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 225 nm,
- injection volume: 10 µl.

Inject the reference solution. The test is not valid unless the column efficiency is not less than 2000 theoretical plates, the tailing factor is not more than 1.5 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 $C_{21}H_{25}ClO_6$.

Storage. Store protected from moisture, at a temperature 2° to 8°.

Dapagliflozin:

Solubility: Freely soluble in *dimethylsulfoxide*, soluble in *ethanol (95 per cent)* and slightly soluble in *water*.