Vildagliptin Prolonged-release 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.	

Vildagliptin Prolonged-release Tablets

Vildagliptin Sustained-release Tablets; Vildagliptin Extended-release Tablets

Vildagliptin Prolonged-release Tablets contain not less than 95.0 per cent and not more than 105.0 per cent of the stated amount of Vildagliptin, $C_{17}H_{25}N_3O_2$.

Usual strengths. 100 mg.

Identification

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

Tests

Dissolution (2.5.2).

Apparatus No. 1 (Basket),
Medium. 1000 ml of *water.*
Speed and time. 50 rpm and 30 minutes, 2 hours, 6 hours, 18 hours.

Withdraw a suitable volume of the medium and filter.

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

Reference solution. Dissolve a suitable quantity of *vildagliptin IPRS* in dissolution medium, and dilute with the dissolution medium to obtain a solution having a known concentration similar to the test solution.

Chromatographic system
- a stainless steel column 5.0 cm ~~15 cm~~ x 4.6 mm, packed with octadecylsilane bonded to porous silica (3.5 µm), (Such as Xterra MS C-18, 120 Å),
- column temperature: 35°,
- mobile phase. A mixture of 90 volumes of a buffer solution prepared by dissolving 1.3 g of *potassium dihydrogen phosphate* in 1000 ml of *water*, adjusted to pH 6.5 with 15 per cent w/v solution *dipotassium hydrogen phosphate* and 10 volumes of *acetonitrile*,
- flow rate: 1.5 ml per minute,
- spectrophotometer set at 210 nm,
- injection volume: 20 µl.

Inject the reference solution. The test is not valid unless the tailing factor is not less than 0.8 and not more than 1.8 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 $C_{17}H_{25}N_3O_2$ in the medium.

At 30 minutes, not more than 20 per cent; at 2 hours, not less than 15 per cent and not more than 40 per cent; at 6 hours, not less than 40 per cent and not more than 70 per cent and at 18 hours, not less than 80 per cent.

Related substances. Determine by liquid chromatography (2.4.14).

Solvent mixture. 90 volumes of *0.02 M hydrochloric acid* and 10 volumes of *methanol*.

Buffer solution. Dissolve 1.3 g of *potassium dihydrogen phosphate* in 1000 ml of *water*, adjusted to pH 6.5 with 15 per cent w/v solution of *dipotassium hydrogen phosphate*.

Test solution. Disperse a quantity of powdered tablets containing 0.6 g of vildagliptin in *methanol* with the aid of ultrasound for 5 minutes with intermittent shaking. Stir the contents for 60 minutes and dilute to 500.0 ml with *methanol*. Centrifuge a portion of the solution at 2000 rpm for 10 minutes. Dilute 10.0 ml of the supernatant liquid to 25.0 ml with *0.02 M hydrochloric acid*, filter.

Reference solution (a). Dissolve 24 mg of *vildagliptin IPRS* in 5 ml of *methanol* and dilute to 50.0 ml with *0.02 M hydrochloric acid*.

Reference solution (b). Dilute 1.0 ml of reference solution (a) to 100.0 ml with the solvent mixture.

Reference solution (c). Dilute 1.0 ml of reference solution (b) to 10.0 ml with the solvent mixture.

Reference solution (d). A solution containing 0.048 per cent w/v of *vildagliptin IPRS* and 0.0005 per cent w/v, each of, vildagliptin impurity A, B and C in the solvent mixture.

Chromatographic system

- a stainless steel column 5.0 cm × 4.6 mm, packed with octadecylsilane bonded to porous silica (3.5 µm), (Such as XTerra MS 120 Å),
- column temperature: 35º,
- mobile phase: A. a mixture of 40 volumes of the buffer solution, 60 volumes of *water*, 1.5 volumes of *methanol* and 1.5 volumes of *acetonitrile*,
  B. a mixture of 40 volumes of the buffer solution, 45 volumes of *acetonitrile* and 15 volumes of *methanol*,
- a gradient programme using the conditions given below,
- flow rate: 1.8 ml per minute,
- spectrophotometer set at 210 nm,
- injection volume: 10 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	100	0
1	100	0
3	90	10
8	30	70
8.1	100	0
15	100	0

Name	Relative retention time	Correction factor
Vildagliptin impurity A[1]	0.63	0.74
Vildagliptin impurity B[2]	0.73	0.88
Vildagliptin	1.0	---
Vildagliptin impurity C[3]	1.13	0.76

[1]2-(3-hydroxy-adamantan-1-yl)-1-imino-hexahydro-pyrrolo[1,2-a]pyrazin-4-one. (Cyclic amidine),
[2](S)1-[(3-Hydroxyadamant-1-ylamino)-acetyl]-2-prolinamide. (Amide),
[3]2-(3-Hydroxy adamantan-1-yl)-hexahydro-pyrrolo[1,2-a]pyrazine-1,4-dione. (Diketopiperazine).

Inject reference solution (b), (c) and (d). The test is not valid unless the resolution between the peaks due to vildagliptin impurity A and vildagliptin impurity B is not less than 2.5 in the chromatogram obtained with reference solution (d), the relative standard deviation for replicate injections is not more than 5.0 per cent in the chromatogram obtained with reference solution (b) and the signal-to-noise ratio is not less than 10 for the principal peak in the chromatogram obtained with reference solution (c).

Inject reference solution (b) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to vildagliptin impurity B is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (2.0 per cent), the area of any peak corresponding to vildagliptin impurity A is not more than 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent), the area of any peak corresponding to vildagliptin impurity C is not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent), the area of any other secondary peak is not more 0.2 times than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent) and the sum of the areas of all the secondary peaks is not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (3.0 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 (b) (0.1 per cent).

Microbial contamination (2.2.9). Total mitiobial count not more than 1000 cfu per g, total yeast and mould count not more than 100 cfu per g, 1g is free from *Escherichia coli,*

Other tests. Comply with the tests stated under Tablets.

Assay. Determine by liquid chromatography (2.4.14), as described under Related substances with the following modifications.

Inject reference solution (a). The test is not valid unless the relative standard deviation for replicate injections is not more than 2.0 per cent and the tailing factor is not less than 0.8 and not more than 1.8.

Inject reference solution (a) and the test solution.

Calculate the content of $C_{17}H_{25}N_3O_2$ in the tablets.

Storage. Store protected at a temperature not exceeding 30º.