Vildagliptin and Metformin 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.

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Vildagliptin and Metformin Prolonged-release Tablets

Vildagliptin and Metformin Hydrochloride Prolonged-release Tablets; Vildagliptin and Metformin Hydrochloride Sustained-release Tablets; Vildagliptin and Metformin Hydrochloride Extended-release Tablets

Vildagliptin and Metformin Tablets contain not less than 90.0 per cent and not more than 110.0 per cent of the stated amounts of vildagliptin, $C_{17}H_{25}N_3O_2$ and metformin hydrochloride, $C_4H_{11}N_5$, HCl.

Usual strengths. Vildagliptin, 50 mg and Metformin hydrochloride, 500 mg; Vildagliptin, 50 mg and Metformin hydrochloride, 850 mg; Vildagliptin, 50 mg and Metformin hydrochloride, 1000 mg.

Identification

In the Assay, the principal peaks in the chromatogram obtained with test solution (a) and test solution (b) correspond to the principal peaks in the chromatogram obtained with the reference solution.

Tests

Dissolution (2.5.2).

For Vildagliptin —

Apparatus No. 2 (Paddle),
Medium. 900 ml of *0.1 M hydrochloric acid*,
Speed and time. 75 rpm and 45 minutes.

Withdraw a suitable volume of the medium and filter.

Determine by liquid chromatography (2.4.14).

Solvent mixture. 85 volumes of *water* and 15 volumes of *acetonitrile*.

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

Reference solution. A 0.055 per cent w/v solution of *vildagliptin IPRS* in the solvent mixture. Dilute 5.0 ml of the filtrate to 50.0 ml with the dissolution medium.

Chromatographic system

- a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm), (Such as X bridge C18),
- column temperature: 35º,
- mobile phase: a mixture of 85 volumes of a buffer solution prepared by dissolving 0.25 g of *sodium octane-1- sulphonic acid andhydrous* in 1000 ml of *water*, add 2 ml of *triethylamine*, adjusted to pH 3.0 with *orthophosphoric acid* and 15 volumes of *acetonitrile*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 210 nm,
- injection volume: 10 µl.

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

Q. Not less than 75 per cent of the stated amount of $C_{17}H_{25}N_3O_2$.

For Metformin Hydrochloride —

Apparatus No. 2 (Paddle),
Medium. 1000 ml of *phosphate buffer pH 6.8*,
Speed and time. 50 rpm and 30 minutes, 2 hours and 12 hours.

Withdraw a suitable volume of the medium and filter.

Determine by liquid chromatography (2.4.14).

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

Reference solution. Dissolve a quantity of *metformin hydrochloride IPRS* in the dissolution medium and dilute to obtain a solution having a known concentration similar to the expected concentration of 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 X bridge C18),
- column temperature: 35º,
- mobile phase: a mixture of 85 volumes of a buffer solution prepared by dissolving 0.25 g of *sodium octane-1- sulphonic acid andhydrous* in 1000 ml of *water*, add 2 ml of *triethylamine*, adjusted to pH 3.0 with *orthophosphoric acid* and 15 volumes of *acetonitrile*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 10 µl.

Inject the reference solution. The test is not valid unless 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 $C_4H_{11}N_5$, HCl in the medium.

Not less than 30.0 per cent after 30 minutes, Not less than 35.0 per cent to 65.0 per cent after 2 hours and Not less than 80.0 per cent after 12 hours of the stated amount of $C_4H_{11}N_5$,HCl.

The percentages of the labeled amount of metformin hydrochloride, $C_4H_{11}N_5$,HCl dissolved at the times specified confirm to 2.5.2. Dissolution test. Acceptance Table 2.

Related substances. Determine by liquid chromatography (2.4.14).

For Vildagliptin —

Solvent mixture. 87 volumes of 0.1 per cent v/v of *perchloric acid* (70 per cent) in *water*, 10 volumes of *acetonitrile* and 3 volumes of *methanol.*

Test solution. Disperse a quantity of the powdered tablets containing of 200 mg of Vildagliptin in the solvent mixture, with the aid of ultrasound for 45 minutes with intermittent shaking and dilute to 200.0 ml with the solvent mixture, filter.

Reference solution. A 0.0005 per cent w/v solution of *vildagliptin IPRS* in the solvent mixture.

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (3 µm) (Such as Inert Sustain),
- sample temperature: 20º,
- column temperature: 35º,
- mobile phase A: a 0.3 per cent v/v of *perchloric acid* (70 per cent) in *water*,
  B: a mixture of 10 volumes of *methanol* and 90 volumes of *acetonitrile*,
- a gradient programme using the conditions given below,
- flow rate: 1 ml per minute,
- spectrophotometer set at 210 nm,
- injection volume: 20 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	96	4
20	96	4
43	69	31
50	45	55
55	45	55
57	96	4
65	96	4

Name	Relative retention time	Correction factor
Vildagliptin impurity B[1]	0.87	0.84
Vildagliptin impurity A[2]	0.9	0.95
Vildagliptin	1.0	---
Vildagliptin impurity C[3]	1.2	0.69

[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 the reference solution. The test is not valid unless the relative standard deviation for 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 peak corresponding to vildagliptin impurity A vildagliptin impurity B and vildagliptin impurity C, each of, is not more than twice the area of principal peak in the chromatogram obtained with the reference solution (1.0 per cent), the area of any other 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 principal peak in the chromatogram obtained with the reference solution (2.0 per cent). Ignore the peaks due to metformin hydrochloride and metformin hydrochloride related impurities and any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with the reference solution (0.05 per cent).

For Metformin Hydrochloride —

Solvent mixture. 85 volumes of *water* and 15 volumes of *acetonitrile*.

Test solution. Disperse a quantity of powdered tablets containing of 1 g of Metformin hydrochloride in *methanol*, with the aid of ultrasound for 45 minutes with intermittent shaking and dilute to 250.0 ml with *methanol*. Dilute 5.0 ml of the solution to 10.0 ml with the solvent mixture, filter.

Reference solution (a). A 0.0002 per cent w/v solution of *metformin hydrochloride IPRS* in the solvent mixture.

Reference solution (b). A 0.0005 per cent w/v solution of *dicyandiamide IPRS* in the solvent mixture.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (3.0 µm) (Such as Inert Sustain),
- column temperature: 40º,
- mobile phase A: a buffer solution prepared by dissolving 1.0 g of *sodium octane-1- sulphonic acid andhydrous* in 1000 ml of *water*, add 1 ml of *triethylamine*, adjusted to pH 3.0 with *orthophosphoric acid*
  B: *acetonitrile*,
- a gradient programme using the conditions given below,
- flow rate: 1 ml per minute,
- spectrophotometer set at 232 nm,
- injection volume: 10 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	85	15
22	85	15
27	35	65
35	35	65
35.1	85	15
56	85	15

Inject reference solution (a). The test is not valid unless the relative standard deviation for six replicate injections is not more than 5.0 per cent.

Inject reference solution (a), (b) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to dicyandiamide (1-cyanoguanidine) is not more than 0.8 times the area of dicyandiamide peak in the chromatogram obtained with reference solution (b) (0.02 per cent), the area of any other secondary peak is not more than 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 6 times the area of principal peak in the chromatogram obtained with reference solution (a) (0.6 per cent). Ignore the peaks due to vildagliptin and vildagliptin related impurities and any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.01 per cent).

Uniformity of content. Complies with the test stated under Tablets.

Determine by liquid chromatography (2.4. 14), as described under Assay, using the following modifications.

Solvent mixture. 85 volumes of *water* and 15 volumes of *acetonitrile*.

Test solution. Disperse one intact tablet in the *methanol*, with the aid of ultrasound for 45 minutes with intermittent shaking and dilute to 250.0 ml with the *methanol.* Dilute 5.0 ml of the solution to 20.0 ml with the solvent mixture, filter.

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

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.

Inject the reference solution and the test solution.

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

Other tests. Comply with the tests stated under Tablets.

Assay. Determine by liquid chromatography (2.4.14),

Solvent mixture. 85 volumes of *water* and 15 volumes of *acetonitrile*.

Test solution (a). Disperse 10 intact tablets in *methanol*, with the aid of ultrasound for 45 minutes with intermittent shaking and dilute to 500.0 ml with *methanol*. Centrifuge to get a clear supernatant, filter. Dilute 10.0 ml of the solution to 20.0 ml with the solvent mixture.

Test solution (b). Dilute a suitable volume of test solution (a) with the solvent mixture to obtain a solution having 0.02 per cent w/v of Metformin Hydrochloride.

Reference solution. A solution containing 0.05 per cent w/v of *vildagliptin IPRS* and 0.02 per cent w/v of *metformin hydrochloride IPRS* in the solvent mixture.

Chromatographic system

- a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (3.0 µm) (Such as Waters, X bridge),
- column temperature: 35º,
- mobile phase: a mixture of 85 volumes of a buffer solution prepared by dissolving 0.25 g of *sodium octane-1-sulphonic acid andhydrous* in 1000 ml of *water*, add 2 ml of *triethylamine*, adjusted to pH 3.0 with *orthophosphoric acid* and 15 volumes of *acetonitrile*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 210 nm (for vildagliptin) and 254 nm (for metformin hydrochloride),
- injection volume: 10 µl.

Inject the reference solution. The test is not valid unless the relative standard deviation for replicate injections is not more than 2.0 per cent, for both the peaks.

Inject the reference solution and test solution (a) and (b).

Calculate the content of $C_{17}H_{25}N_3O_2$ in test solution (a) and $C_4H_{11}N_5$, HCl in test solution (b) in the tablets.

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