Azilsartan and Chlorthalidone 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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Azilsartan and Chlorthalidone Tablets

Azilsartan Medoxomil and Chlorthalidone Tablets

Azilsartan and Chlorthalidone Tablets contain azilsartan kamedoxomil equivalent to not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of azilsartan medoxomil, $C_{30}H_{24}N_4O_8$ and chlorthalidone, $C_{14}H_{11}ClN_2O_4S$.

Usual strengths. Azilsartan medoxomil, 40 mg and Chlorthalidone 25 mg; Azilsartan medoxomil, 40 mg and Chlorthalidone 12.5 mg; Azilsartan medoxomil, 40 mg and Chlorthalidone 6.25 mg.

Identification

In the Assay, the principal peaks in the chromatogram obtained with the test solution correspond to the principal peaks in the chromatogram obtained with the reference solution.

Tests

Dissolution (2.5.2).

Apparatus. No. 2 (Paddle),
Medium. 900 ml of phosphate buffer pH 6.8 containing 1.0 per cent w/v of *sodium lauryl sulphate*,
Speed and time. 75 rpm and 45 minutes.

Withdraw a suitable volume of the medium and filter.

Determine by liquid chromatography (2.4.14).

Test solution. Dilute 5.0 ml of the filtrate to 10.0 ml with the mobile phase.

Reference solution (a). A 0.0235 per cent w/v solution of *azilsartan kamedoximil IPRS* in the mobile phase.

Reference solution (b). A 0.00696 per cent w/v solution of *chlorthalidone IPRS in the mobile phase.*

Reference solution (c) Dilute a suitable volume of reference solution (a) and reference solution (b) with the mobile phase to obtain a solution having similar concentration to that of the test solution.

Chromatographic system.

-A stainless steel column 25 cm x 4.6 mm packed with octadecylsilane bonded to porous silica (5 µm) (Such as phenomenex luna C-18 (2)),

-mobile phase: a mixture of 40 volumes of a buffer solution prepared by dissolving 2.72 g of *potassium dihydrogen orthophosphate* in 1000 ml of *water*, adjusted to pH 3.0 with *dilute orthophosphoric acid* and 60 volumes of *acetonitrile*,

-Flow rate: 1 ml per minute,

-Spectrophotometer set at 243 nm,

-Injection volume: 20 µl.

Inject the reference solution (c). The test is not valid unless the column efficiency is not less than 2000 theoretical plates, 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 for both the peaks.

Inject reference solution (c) and the test solution.

Calculate the content of $C_{30}H_{24}N_4O_8$ and $C_{14}H_{11}ClN_2O_4S$ in the medium.

Q. Not less than 70 per cent of the stated amounts of $C_{30}H_{24}N_4O_8$ and $C_{14}H_{11}ClN_2O_4S$.

Related substances. Determine by liquid chromatography (2.4.14).

NOTE- Prepare the solutions immediately before use.

Buffer solution. Dissolve 3.0 g *of sodium perchlorate monohydrate* in 1000 ml of *water*, add 3.0 ml of *triethylamine*, adjusted to pH 3.0 with *dilute orthophosphoric acid.*

Solvent mixture. 55 volumes of the buffer solution and 45 volumes of *acetonitrile*.

Test solution. Disperse a quantity of the powdered tablets containing 100 mg of azilsartan medoxomil in the solvent mixture with the aid of ultrasound for 15 minutes with intermittent shaking and dilute to 100.0 ml with the solvent mixture, filter.

Reference solution. A solution containing 0.00027 per cent w/v of *azilsartan kamedoxomil IPRS* and 0.001 per cent w/v of *azilsartan kamedoximil impurity B IPRS* in the solvent mixture,

Chromatographic system

–a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (Such as Phenomenex luna C-18 (2)

–mobile phase: A. the buffer solution,

B. *acetonitrile*,

–a gradient programme using the conditions given below,

–flow rate: 1.2 ml per minute,

–spectrophotometer set at 254 nm,

–injection volume: 20 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	55	45
5	50	50
15	45	55
30	45	55
45	55	45
60	55	45

Name	Relative retention time
Azilsartan kamedoxomil impurity B[1] *	0.47
Azilsartan kamedoxomil	1.00

[1]2-ethoxy-1-{[2-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]}methyl)-1H-benzo [d] imidazole-7-carboxylic acid (Azilsartan)

Inject the reference solution. The test is not valid unless the resolution between the peaks due to azilsartan and azilsartan kamedoxomil impurity B is not less than 5.0, the column efficiency is not less than 2000 theoretical plates and the tailing factor is not more than 2.0 for both the peaks.

Inject the reference solution and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to azilsartan kamedoxomil impurity B is not more than twice the area of the corresponding peak in the chromatogram obtained with the reference solution (2.0 per cent), the area of any other secondary peak is not more than twice the area of the principal peak in the chromatogram obtained with the reference solution (0.5 per cent) and the sum of areas of all the secondary peaks other than azilsartan kamedoxomil impurity B is not more than 8 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).

Test Solution. Weigh and powder 20 tablets. Disperse a quantity of the powder containing 0.2 g of Azilsartan Medoxomil in the mobile phase with the aid of ultrasound with intermittent shaking and dilute to 250.0 ml with mobile phase. Dilute 5.0 ml of the solution to 50.0 ml with the mobile phase. Dilute with mobile phase, if necessary, to obtain a solution having similar concentration to that of the reference solution.

Reference solution. A solution containing 0.0854 per cent w/v of *azilsartan kamedoxomil IPRS* and 0.0125 per cent w/v of *chlorthalidone IPRS* in the mobile phase. Dilute 5.0 ml of the solution to 50.0 ml with the mobile phase.

Use the chromatographic system as described under Dissolution.

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 2.0 and the relative standard deviation for replicate injections is not more than 2.0 per cent, for both the peaks.

Inject the reference solution and the test solution.

Calculate the contents of $C_{30}H_{24}N_4O_8$ and $C_{14}H_{11}ClN_2O_4S$ in the tablets.

1 mg of azilsartan kamedoxomil, $C_{30}H_{23}KN_4O_8$ is equivalent to 0.9372 mg of azilsartan medoxomil, $C_{30}H_{24}N_4O_8$.

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

Labelling. The label states the quantity of azilsartan kamedoxomil in the term of the equivalent amount of azilsartan medoxomil and chlorthalidone**.**