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Draft Proposal for Comments and Inclusion in The Indian Pharmacopoeia

Azilsartan Kamedoxomil

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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

Description	Details
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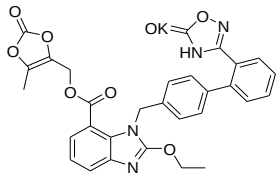
Further follow-up action as required.	

Azilsartan Kamedoxomil



$C_{30}H_{23}KN_4O_8$ Mol. Wt. 606.6

Azilsartan Kamedoxomil is (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-1H benzimidazole-7-carboxylate monopotassium salt.

Azilsartan Kamedoxomil contains not less than 98.0 per cent and not more than 102.0 per cent of $C_{30}H_{23}KN_4O_8$, calculated on the anhydrous basis.

Category. Antihypertensive.

Description. A white to off-white powder.

Identification

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

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

NOTE —Perform the tests and assay using low-actinic glassware.

Potassium. 6.0 per cent to 7.0 per cent, determined on anhydrous basis.

Dissolve 0.5 g in 100 ml of *methanol* with the aid of ultrasound and add 20 ml of *water*. Titrate with *0.1 M hydrochloric acid*, determining the end-point potentiometrically (2.4.25). Carry out a blank titration.

1 ml of *0.1 M hydrochloric acid* is equivalent to 0.00391 g of potassium.

Related substances. Determine by liquid chromatography (2.4.14).

Solvent mixture. 100 volumes of *acetonitrile* and 0.5 volume of *formic acid.*

Test solution. Dissolve 60 mg of the substance under examination in the solvent mixture and dilute to 50.0 ml with the solvent mixture.

Reference solution (a). A 0.00562 per cent w/v solution of *azilsartan medoxomil IPRS* in the solvent mixture. Dilute 1.0 ml of the solution to 10.0 ml with the solvent mixture.

Reference solution (b). A solution containing 0.12 per cent w/v of *azilsartan medoxomil IPRS* and 0.00018 per cent w/v, each of, *azilsartan kamedoxomil impurity G IPRS* and *azilsartan kamedoxomil impurity H IPRS* in the solvent mixture.

Reference solution (c). A solution containing 0.12 per cent w/v of *azilsartan kamedoxomil IPRS*, 0.00036 per cent w/v *azilsartan kamedoxomil impurity B IPRS* and 0.00018 per cent w/v, each of, *azilsartan kamedoxomil impurity A IPRS, azilsartan kamedoxomil impurity C IPRS, azilsartan kamedoxomil impurity D IPRS, azilsartan kamedoxomil impurity E IPRS* and *azilsartan kamedoxomil impurity F IPRS* in the solvent mixture.

Chromatographic system

- a stainless steel column 15 cm × 4.6 mm, packed with octadecylsilane bonded to porous silica (3 µm), (Such as YMC-Pack Pro C18),
- sample temperature: 15º,
- mobile phase: A. a mixture of 90 volumes of *water*, 10 volumes of *acetonitrile* and 0.1 volume of *formic acid*,
  B. a mixture of 10 volumes of *water*, 90 volumes of *acetonitrile* and 0.05 volume of *formic acid,*
- a gradient programme using the conditions given below,
- flow rate: 1.25 ml per minute,
- spectrophotometer set at 254 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
5	65	35
12	60	40
28	30	70
38	0	100
48	0	100
49	80	20
55	80	20

Name	Relative retention time	Correction factor
Azilsartan kamedoxomil impurity A[1]	0.31	0.75
Azilsartan kamedoxomil impurity B[2]	0.57	0.81
Azilsartan kamedoxomil impurity C[3]	0.63	--
Azilsartan kamedoxomil impurity D[4]	0.76	0.95
Azilsartan kamedoxomil impurity E[5]	0.93	0.81
Azilsartan kamedoxomil	1.0	----
Azilsartan kamedoxomil impurity F[6]	1.06	0.83
Azilsartan kamedoxomil impurity G[7]	1.23	1.11
Azilsartan kamedoxomil impurity H[8]	1.25	0.79
Dimer-3	1.60	0.92

[1]2-oxo-3((2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-[1,1'-biphenyl]-4-yl)methyl)-2,3-dihydro-1H-benzo[d] imidazole-4-carboxylic acid. (Desethyl Asilsartan).
[2]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. (Asilsartan).
[3](5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 2hydroxy-1-((2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3yl)-[1,1'-biphenyl]-4-yl)methyl)-1H-benzo[d] imidazole-7-carboxylate. (Desethyl Azilsartan Medoxomil).
[4] (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 1-((2'carbamoyl-[1,1'-biphenyl]-4-yl)methyl)-2-ethoxy-1H-benzo[d] imidazole -7-carboxylate.
[5]methyl 2-ethoxy-1-((2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-[1,1'-biphenyl]-4-yl)methyl)-1H-benzo[d] imidazole-7-carboxylate. (methyl Ester).
[6]ethyl 2-ethoxy-1- ((2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-[1,1'-biphenyl]-4-yl)methyl)-1H-benzo[d] imidazole-7-carboxylate.
[7] (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl) 2-ethoxy-1-((2'-(4-((5methyl-2-oxo-1,3-dioxol-4-yl)methyl5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-[1,1'-biphenyl]-4yl)-4-yl)methyl)-1H-benzo[d]imidazole-7-carboxylate. (Bis impuity).
[8]7-(((5-methyl-2-oxo-1,3-dioxol-4-yl)methoxy)carbonyl)-1-((2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3yl)-[1,1'-biphenyl]-4-yl)methyl)-1H-benzo[d] midazole-2yl 2-etoxy-1-((2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-[1,1'-biphenyl]-4yl)-4-yl)methyl)-1H-benzo[d]imidazole-7-carboxylate. (Azilsartan Medoxomil Dimer-4).

Inject reference solution (b) and (c) to identify the peaks due to azilsartan kamedoxomil impurity G, H and azilsartan kamedoxomil impurity A, B, C, D, E and F respectively.

Inject reference solution (a) and (b). The test is not valid unless the resolution between the peaks due to azilsartan kamedoxomil impurity G and azilsartan kamedoxomil impurity H is not less than 1.4 in the chromatogram obtained with reference solution (b) and the relative standard deviation for replicate injections is not more than 5.0 per cent in the chromatogram obtained with reference solution (a).

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution the area of any peak corresponding to azilsartan kamedoxomil impurity A, azilsartan kamedoxomil impurity C, azilsartan kamedoxomil impurity D, azilsartan kamedoxomil impurity E, azilsartan kamedoxomil impurity F, azilsartan kamedoxomil impurity G and azilsartan kamedoxomil impurity H, 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 peak corresponding to azilsartan kamedoxomil impurity B is not more than 0.6 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 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 twice the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 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 (a) (0.05 per cent).

Heavy metals (2.3.13). 1.0 g complies with the limit test for heavy metals, Method B (20 ppm).

Water (2.3.43). Not more than 0.8 per cent, determined on 1.0 g.

Microbial contamination (2.2.9). Total aerobic viable count is not more than 1000 CFU and total fungal count is not more than 100 CFU per g. 1g is free from *Escherichia coli*.

Assay. Determine by liquid chromatography (2.4.14).

Solvent mixture. 100 volumes of *acetonitrile* and 0.5 volumes of *formic acid.*

Solution A. a mixture of 90 volumes of *water*, 10 volumes of *acetonitrile* and 0.1 volume of *formic acid,*

Solution B. a mixture of 10 volumes of *water*, 90 volumes of *acetonitrile* and 0.05 volume of *formic acid,*

Test solution. Dissolve 0.12 g of the substance under examination in the solvent mixture and dilute to 100.0 ml with the solvent mixture. Dilute 2.0 ml of the solution to 10.0 ml with the solvent mixture.

Reference solution. A 0.0225 per cent w/v solution of *azilsartan medoxomil IPRS* in the solvent mixture.

Chromatographic system
- a stainless steel column 15 cm × 4.6 mm, packed with octadecylsilane bonded to porous silica (3 µm), (Such as YMC-Pack Pro C18),
- sample temperature: 15º,
- mobile phase: a mixture of 45 volumes of solution A and 55 volumes of solution B,
- flow rate: 1.25 ml per minute,
- spectrophotometer set at 254 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 injection is not more than 1.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{30}H_{23}KN_4O_8$.
1 mg of $C_{30}H_{24}N_4O_8$ is equivalent to 1.067 mg of $C_{30}H_{23}KN_4O_8$.

Storage. Store protected from light and moisture, at a temperature not exceeding 30°.

Azilsartan Kamedoxomil

Solubility: Sparingly soluble in *methanol*, slightly soluble in *N,N dimethylformamide* and practically insoluble in *water*.