Bilastine

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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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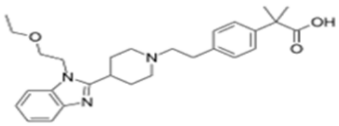
Bilastine



$C_{28}H_{37}N_3O_3$ Mol. Wt. 463.6

Bilastine is 2-[4-(2-(4-(1-(2-ethoxyethyl)-benzimidazole-2-yl)piperidine-1-yl)ethyl)phenyl]-2methylpropanoic acid.

Bilastine contains not less than 98.0 per cent and not more than 102.0 per cent of $C_{28}H_{37}N_3O_3$, calculated on the dried basis.

Category. Antihistaminic.
Description. A white to creamy white powder.

Identification

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

Related substances. Determine by liquid chromatography (2.4.14).

Solvent mixture. 60 volumes of *water* and 40 volumes of *acetonitrile*.

Test solution. Dissolve 50 mg of the substance under examination in the solvent mixture and dilute to 100.0 ml with the solvent mixture.

Reference solution (a). A 0.005 per cent w/v solution of *bilastine IPRS* in the solvent mixture. Dilute 1.0 ml of the solution to 100.0 ml with the solvent mixture.

Reference solution (b). A solution containing 0.5 per cent w/v of *bilastine IPRS* and 0.00075 per cent w/v, each of, *bilastine impurity A IPRS, bilastine impurity B IPRS, bilastine impurity C IPRS, bilastine impurity D IPRS, bilastine impurity E IPRS* and *bilastine impurity F IPRS* in the solvent mixture. Dilute 1.0 ml of the solution to 10.0 ml with 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 Inertsil ODS 3V),
- column temperature: 45°,
- mobile phase: A. a mixture of 90 volumes of a buffer solution prepared by dissolving 1.56 g of *dipotassium hydrogen phosphate anhydrous* in 1000 ml of *water*, adjusted to pH 7.0 with *dilute orthophosphoric acid* and 10 volumes of *acetonitrile*,
  B. a mixture of 90 volumes of *acetonitrile* and 10 volumes of *methanol*,
- a gradient programme using the conditions given below,
- flow rate: 1 ml per minute,
- spectrophotometer set at 215 nm,
- injection volume: 20 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	90	10
6	90	10
20	80	20
40	60	40
70	40	60

85	40	60
87	90	10
95	90	10

Name	Relative retention time	Correction factor
Bilastine impurity A[1]	0.47	1.02
Bilastine impurity B[2]	0.75	---
Bilastine impurity F[3]	0.84	1.02
Bilastine	1.00	---
Bilastine impurity C[4]	1.61	1.12
Bilastine impurity D[5]	1.98	1.05
Bilastine impurity E[6]	2.03	---

[1]2-(4-(2-(4-(1-(2-hydroxyethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)ethyl)phenyl)-2-methylpropanoic acid,
[2]1-(4-(2-carboxypropan-2-yl)phenethyl)-4-(1-(2-ethoxyethyl)-1H-benzo[d]imidazol-2-yl)piperidine 1-oxide,
[3]2-(4-(2-(4-(1-(2-methoxyethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)ethyl)phenyl)-2-methylpropanoic acid.
[4]2-(4-(2-(4-(1-(2-ethoxyethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)ethyl)phenyl)-N-(1-hydroxy-2-methylpropan-2-yl)-2-methylpropanamide,
[5]2-(2-(4-(2-(4-(1-(2-ethoxyethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)ethyl) phenyl) propan-2-yl)-4,4-dimethyl-4,5-dihydrooxazole,
[6]Methyl-2-(4-(2-(4-(1-(2-ethoxyethyl)-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)ethyl)phenyl)-2-methylpropanoate,

Inject reference solution (a) and (b). The test is not valid unless the resolution between the peaks due to bilastine impurity D and E is not less than 1.2 in the chromatogram obtained with reference solution (b), the column efficiency is not less than 50000 theoretical plates, the tailing factor is not more than 2.0 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 bilastine impurity A, B, C, D, E, and F, each of, is not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent), the area of any other secondary peak is not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent) and the sum of the areas of all the secondary peaks is not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent). Ignore any peak corresponding to toluene (at relative retention time about 1.62) and with an area less than 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.03 per cent).

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

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

Loss on drying (2.4.19). Not more than 1.0 per cent, determined on 1.0 g by drying in an oven at 105° for 3 hours.

Assay. Determine by liquid chromatography (2.4.14).
Test solution. Dissolve 50.0 mg of the substance under examination in the solvent mixture and dilute to 100.0 ml with the solvent mixture. Dilute 5.0 ml of the solution to 25.0 ml with the solvent mixture.

Reference solution. A 0.01 per cent w/v solution of *bilastine IPRS* in the solvent mixture.

Use the chromatographic system as described under Related substances with the following modifications.
- flow rate:1.5 ml per minute,

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	90	10
24	66	34
25	35	65
34	35	65

35	90	10
40	90	10

Inject the reference solution. The test is not valid unless the column efficiency is not less than 10000 theoretical plates, the tailing factor is not more than 2.0 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 $C_{28}H_{37}N_3O_3$.

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

2.4.26. Solubility.

Insert before **Biotin.** Page 268

Solubility. Slightly soluble in *methanol*, very slightly soluble in *dimethyl sulphoxide* and practically insoluble in *water*.