Bendamustine Hydrochloride

Published on: 07 February, 2024 **Last date for comments:** 22 March, 2024

This draft proposal contains monograph text for inclusion in the Indian Pharmacopoeia (IP). The content of this draft document is not final, and the text may be subject to revisions before publication in the IP. This draft does not necessarily represent the decisions or the stated policy of the IP or Indian Pharmacopoeia Commission (IPC).

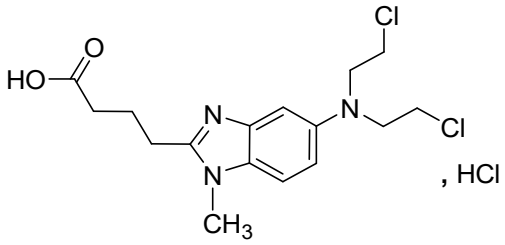
Manufacturers, regulatory authorities, health authorities, researchers, and other stakeholders are invited to provide their feedback and comments on this draft proposal. Manufacturers are also invited to submit samples of their products to the IPC to ensure that the proposed monograph adequately controls 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
Document version	1.0
First draft published on IPC website for public comments	February 7, 2024
Last date for comments	**March 22, 2024**
Monograph revisions proposed for inclusion in	**IP 2026**
Tentative effective date of monograph revisions	**July, 2026**
Draft revision published on IPC website for public comments	--
Further follow-up action as required.	

Bendamustine Hydrochloride. Page 1586
Change **to**: **Bendamustine Hydrochloride**



$C_{16}H_{21}Cl_2N_3O_2$, HCl — Mol Wt. 394.7
$C_{16}H_{21}Cl_2N_3O_2$, HCl, H_2O — Mol Wt. 412.7

Bendamustine Hydrochloride is 4-{5-[Bis(2-chloroethyl)amino]-1-methyl-1*H*-benzimidazole-2-yl}butanoic acid monohydrochloride.

Bendamustine Hydrochloride is anhydrous or monohydrate. The anhydrous form of Bendamustine Hydrochloride contains not less than 98.0 per cent and not more than 102.0 per cent of $C_{16}H_{21}Cl_2N_3O_2$.HCl, calculated on the as-is basis. The monohydrate form of Bendamustine Hydrochloride contains not less than 98.0 per cent and not more than 102.0 per cent of $C_{16}H_{21}Cl_2N_3O_2$.HCl, calculated on the anhydrous and solvent-free basis.

Category. Antineoplastic.

Description. A white to almost white powder.

Identification

A. Determine by infrared absorption spectrophotometry. Compare the spectrum with that obtained with *bendamustine hydrochloride IPRS* or with the reference spectrum of bendamustine hydrochloride.

B. 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).

C. It gives reaction (A) of chlorides (2.3.1).

Tests

Related substances. Determine by liquid chromatography (2.4.14).

Solvent mixture. Equal volumes of *1-methyl-2-pyrrolidone* and mobile phase A.

Test solution. Dissolve 42 mg of the substance under examination in the solvent mixture and dilute to 10.0 ml with the solvent mixture.

Reference solution (a). A 0.42 per cent w/v solution of *bendamustine hydrochloride IPRS* in the solvent mixture.

Reference solution (b). Dilute 1.0 ml of reference solution (a) to 100.0 ml with the solvent mixture. Dilute 1.0 ml of the solution to 10.0 ml with the solvent mixture.

Reference solution (c). A solution containing 0.42 per cent w/v of *bendamustine hydrochloride IPRS* and 0.002 per cent w/v, each of, *bendamustine related compound A IPRS*, *bendamustine related compound C IPRS*, *bendamustine related compound D IPRS*, *bendamustine related compound E IPRS*, *bendamustine related compound G IPRS*, *bendamustine related compound H IPRS*, and *bendamustine related compound I IPRS* in the solvent mixture.

Reference solution (d). Dilute 5.0 ml of reference solution (b) to 10.0 ml with the solvent mixture.

Chromatographic system

- a stainless steel column 15 cm x 4.6 mm, packed with endcapped alkyl amide group bonded to spherical porous silica (5µm) (Such as Bonus- RP),
- sample temperature: 2°-8°,
- mobile phase: A. a 0.1 per cent v/v solution of *trifluoroacetic acid* in *water*,
  B. a 0.1 per cent v/v solution of *trifluoroacetic acid* in *acetonitrile*,
- a gradient programme using the conditions given below,
- flow rate: 1 ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 2 µl.

Time (in min.)	Mobile phase A (Per cent v/v)	Mobile phase B (Per cent v/v)
0	93	7
5	93	7
13	73	27
16	73	27
25	43	57
26	10	90
31	10	90
40	93	7
45	93	7

Name	Relative retention time	Correction factor
Bendamustine impurity A[1]	0.25	1.32
Bendamustine impurity C[2]	0.60	1.20
Bendamustine impurity D[3]	0.69	1.08
Bendamustine impurity E[4]	0.73	0.83
Bendamustine impurity G[5]	0.90	0.32
Bendamustine	1.0	---
Bendamustine impurity H[6]	1.15	1.02
Bendamustine impurity I[7]	1.20	0.91

[1]4-{5-[Bis(2-hydroxyethyl)amino]-1-methyl-1*H*-benzimidazol-2-yl}butanoic acid,
[2]Ethyl 4-{5-[bis(2-hydroxyethyl)amino]-1-methyl-1*H*-benzimidazol-2-yl}butanoate,
[3]4-{5-[(2-Chloroethyl)amino]-1-methyl-1*H*-benzimidazol-2-yl}butanoic acid,
[4]4-{5-[(2-Chloroethyl)(2-hydroxyethyl)amino]-1-methyl-1*H*-benzimidazol-2-yl}butanoic acid,
[5]4-[6-(2-Chloroethyl)-3,6,7,8-tetrahydro-3-methylimidazo[4,5-*h*][1,4]benzothiazin-2-yl]butanoic acid,
[6]4-[5-({2-[(4-{5-[Bis(2-chloroethyl)amino]-1-methyl-1*H*-benzimidazol-2-yl}butanoyl)oxy]ethyl}(2-chloroethyl)amino)-1-methyl-1*H*-benzimidazol-2-yl]butanoic acid,
[7]Ethyl 4-{5-[bis(2-chloroethyl)amino]-1-methyl-1*H*-benzimidazol-2-yl}butanoate.

Inject reference solution (c) and (d). The test is not valid unless the resolution between the peaks due to the bendamustine related compound G and bendamustine is not less than 5 and between bendamustine related compound H and bendamustine related compound I is not less than 4 in the chromatogram obtained with reference solution (c) and the signal-to-noise ratio of the principal peak is not less than 10 in the chromatogram obtained with reference solution (d).

Inject reference solution (b) and the test solution. The area of any peak corresponding bendamustine related compound A is not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.25 per cent), the area of any peak corresponding to bendamustine related compound C is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) 0.20 per cent), the area of any peak corresponding to bendamustine related compound D is not more than 1.5 times the area of the principal peak in the chromatogram

obtained with reference solution (b) 0.15 per cent), the area of any peak corresponding to bendamustine related compound E is not more than 4.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.45 per cent), the area of any peak corresponding to bendamustine related compound G is not more than 3.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.35 per cent), the area of any peak corresponding to bendamustine related compound H is not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.30 per cent), the area of any peak corresponding to bendamustine related compound I is not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (b) in the chromatogram obtained with reference solution (b) (0.40 per cent), the area of any other secondary peak is not more than the area of principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent) and the sum of areas of all the secondary peaks is not more than 10 times the area of the principal peak in the chromatogram obtained with principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent). Ignore any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

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

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

Water (2.3.43). Not more than 1.0 per cent for anhydrous form; 3.0 to 5.5 per cent for monohydrate form.

Bacterial endotoxins (2.2.3). Not more than 1.125 Endotoxin Units per mg of bendamustine hydrochloride.

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

Inject reference solution (a). 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 1.0 per cent.

Inject reference solution (a) and the test solution.

Calculate the content of $C_{16}H_{21}Cl_2N_3O_2.HCl$.

Microbial contamination (2.2.9). Total aerobic viable count is not more than 1000 CFU per g and total moulds and yeasts is not more than 100 CFU per g.

Storage. Store protected from light and moisture, at a temperature between 2° to 8°.