Pimobendan Capsules

Published on: 05 January, 2023 **Last date for comments:** 04 February, 2023

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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
Document version	2.0
Monograph proposed for inclusion	IP Addendum 2024
Tentative effective date of monograph	April, 2024
First draft published on IPC website for public comments	26 August, 2022
Draft revision published on IPC website for public comments	05 January, 2023 (Version 2.0)
Further follow-up action as required.	

Pimobendan Capsules

Pimobendan Capsules contain not less than 95.0 per cent and not more than 105.0 per cent of the stated amount of pimobendan, $C_{19}H_{18}N_4O_2$.

Usual strength. 1.25 mg; 2.5 mg; 5 mg;

Identification

A. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel GF254* (Such as Merck silica gel 60 F_{254}).

Mobile phase. A mixture of 90 volumes of *dichloromethane* and 10 volumes of *methanol.*

Test solution. Disperse a quantity of the mixed content containing 10 mg of Pimobendan in 10 ml in *methanol*. Dilute 1.0 ml of the solution to 20.0 ml in *methanol*.

Reference solution. A 0.005 per cent w/v solution of *pimobendan IPRS* in *methanol.*

Apply to the plate 10 µl of reference solution and test solution. After development, dry the plate in air and examine under ultraviolet light at 254 nm. The principal spots in the chromatogram obtained with the test solution corresponds to that in the chromatogram obtained with the reference solution.

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).

Tests

Dissolution (2.5.2).

Apparatus No. 2 (Paddle),

Medium. 500 ml of *0.01M sodium acetate*, adjusted to pH 5.0 with *glacial acetic acid (for capsules containing 1.25 mg or less);* 900 ml of *0.01M sodium acetate*, adjusted to pH 5.0 with *glacial acetic acid (more than ~~then~~1.25 mg),*

Speed and time. 75 rpm and 45 minutes.

Withdraw a suitable volume of the medium and filter.

Test solution. Use the filtrate, dilute if necessary with *water* to obtain a solution having 0.00025 per cent w/v of pimobendan.

Reference solution. A 0.0025 per cent w/v solution of *pimobendan IPRS* in *methanol.* Dilute 1.0 ml of the solution to 10.0 ml with dissolution medium.

Chromatographic system

- a stainless steel column 6 cm × 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (Such as Nucleosil RP C18),
- column temperature: 40°,
- mobile phase. a mixture of 65 volumes of *0.05M diammonium hydrodegen orthophosphate,* adjusted to pH 5.5 with *orthophosphoric acid* and 35 volumes of *acetonitrile,*
- flow rate: 0.7 ml per minute,
- spectrophotometer set at 328 nm,
- injection volume: 20 µl.

Inject the reference solution and the test solution.

Calculate the content of $C_{19}H_{18}N_4O_2$ in the medium.

Q. Not less than 75 per cent of the stated amount of $C_{19}H_{18}N_4O_2$.

Related substances. Determine by liquid chromatography (2.4.14),

Test solution. Disperse a quantity of the mixed content containing 12.5 mg of Pimobendan in 10 ml of *water*, with the aid of ultrasound and dilute to 50.0 ml with *methanol.* Dilute 1 volume of the solution to 5 volumes with *methanol*.

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

Reference solution (b). A 0.05 per cent w/v solution of *pimobendan for system suitability IPRS* (containing pimobendan impurities A and B) in *methanol.*

Reference solution (c). Dilute 3 volume of reference solution (a) to 10 volumes with *methanol*.

Chromatographic system

- a stainless steel column 12.5 cm × 4.6 mm, packed with end capped octadecylsilane bonded to porous silica (5 µm) (Such as Nucleosil RP C18),
- mobile phase. a mixture of 66 volumes of *0.05M diammonium hydrodegen orthophosphate,* adjusted to pH 5.5 with *orthophosphoric acid* and 34 volumes of *acetonitrile,*
- flow rate: 0.7 ml per minute,
- spectrophotometer set at 328 nm and 312 nm,
- injection volume: 10 µl.

Name	Relative retention time
Pimobendan impurity A [1]	0.6
Pimobendan impurity B [2]	0.7
Pimobendan (retention time: about 5 minutes)	1.0

[1](3*RS*)-4-[2-(4-methoxyphenyl)-1*H*-benzimidazol-5-yl]-3-methyl-4-oxobutanoic acid,
[2](5*RS*)-6-[3-amino-4-(4-methoxybenzamido)phenyl]-5-methyl-4,5-dihydropyridazin-3(2*H*)-one.

Inject reference solution (b) at 328 nm. The test is not valid unless the resolution between the peaks due to pimobendan impurity A and pimobendan impurity B is not less than 1.5.

Inject reference solution (a) and the test solution at 312 nm. In the chromatogram obtained with the test solution, the area of any peak corresponding to pimobendan impurity B is not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent).

Inject reference solution (a), (c) and the test solution at 328 nm. In the chromatogram obtained with the test solution, the area of any peak corresponding pimobendan impurity A is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (2.0 per cent), the area of any other secondary peak is not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent) and the sum of areas of all the secondary peaks is not more than 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 the area of the principal peak in the chromatogram obtained with reference solution (c) (0.3 per cent).

Uniformity of content (2.5.4). Complies with the test stated under Capsules.

Determine by liquid chromatography (2.4.14),

Test solution. Disperse the content of one capsule in 5 ml of *water*. Add 15 ml of *methanol* and mix with the aid of ultrasound for 15 minutes with intermittent shaking and dilute to 25.0 ml with *methanol*, centrifuge and use the clear

supernatant liquid. Dilute the supernatant, if necessary, with *methanol* to obtain a solution having the similar concentration to that of reference solution.

Reference solution (a). A 0.005 per cent w/v solution of *pimobendan IPRS* with *methanol*.

Reference solution (b). A 0.05 per cent w/v solution of *pimobendan for system suitability IPRS* (containing pimobendan impurities A and B) in *methanol.*

Use chromatographic system as described under Related substances with the following modifications

– spectrophotometer set at 328 nm,

Inject reference solution (b). The test is not valid unless the resolution between the peaks due to pimobendan impurity A and pimobendan impurity B is not less than 1.5.

Inject the reference solution and the test solution.

Calculate the content of $C_{19}H_{18}N_4O_2$ in the capsule.

Other tests. Comply with the tests stated under Capsules.

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

Test solution. Weigh and mix the content of 20 capsules. Disperse a quantity of the mixed content containing 25 mg of pimobendan in *methanol* and dilute to 100.0 ml with *methanol.* Dilute 1 volume of the solution to 5 volumes with *methanol*.

Reference solution (a). A 0.005 per cent w/v solution of *pimobendan IPRS* in *methanol.*

Reference solution (b). A 0.015 per cent w/v solution of *pimobendan for system suitability IPRS* (containing pimobendan impurities A and B) in *methanol.*

Use chromatographic system as described under Related substances with the following modifications

– spectrophotometer set at 328 nm,

Inject reference solution (b). The test is not valid unless the resolution between the peaks due to pimobendan impurity A and pimobendan impurity B is not less than 1.5.

Inject reference solution (a) and the test solution.

Calculate the content of $C_{19}H_{18}N_4O_2$ in the capsules.

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