Edition: BP 2025 (Ph. Eur. 11.6 update)

Pimobendan Capsules

General Notices

Action and use

Inhibitor of phosphodiesterase type III; calcium sensitizer.

DEFINITION

Pimobendan Capsules contain Pimobendan.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of pimobendan, $C_{19}H_{18}N_4O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.
(1) Shake a quantity of capsule contents containing 10 mg of Pimobendan with 10 mL of *methanol*. Filter and dilute the filtrate with sufficient *methanol* to produce a solution containing 0.005% w/v of Pimobendan.
(2) 0.005% w/v of pimobendan BPCRS in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).
(b) Use the mobile phase as described below.
(c) Apply 10 µL of each solution.
(d) Develop the plate to 15 cm.
(e) After removal of the plate, dry in air and examine immediately under *ultraviolet light (254 nm)*.

MOBILE PHASE

1 volume of *methanol* and 9 volumes of *dichloromethane*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the requirements in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 75 revolutions per minute.

For capsules containing 1.25 mg or less of Pimobendan

(b) Use 500 mL of 0.01M *sodium acetate*, adjusted to pH 5.0 with *glacial acetic acid*, at a temperature of 37°, as the medium.

For capsules containing more than 1.25 mg of Pimobendan

(b) Use 900 mL of 0.01M *sodium acetate*, adjusted to pH 5.0 with *glacial acetic acid*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a sample of the medium and filter. Use the filtered medium, diluted with water if necessary, to produce a solution expected to contain 0.00025% w/v of Pimobendan.
(2) 0.0025% w/v of *pimobendan BPCRS* in *methanol*. Dilute 1 volume to 10 volumes with the dissolution medium.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (6 cm × 4.0 mm) packed with *end-capped octadecylsilyl silica gel* (5 µm) (Nucleosil RP C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 0.7 mL per minute.
(d) Use a column temperature of 40°.
(e) Use a detection wavelength of 328 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

35 volumes of *acetonitrile* and 65 volumes of 0.05M *diammonium hydrogen orthophosphate*, adjusted to pH 5.5 with *orthophosphoric acid*.

DETERMINATION OF CONTENT

Calculate the total content of $C_{19}H_{18}N_4O_2$, in the medium from the chromatograms obtained and using the declared content of $C_{19}H_{18}N_4O_2$, in *pimobendan BPCRS*.

LIMITS

The amount of pimobendan released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *methanol*.

(1) Disperse a quantity of the capsule contents containing 12.5 mg of Pimobendan in 10 mL of *water* and dilute to 50 mL. Dilute 1 volume of the resulting solution to 5 volumes.
(2) Dilute 1 volume of solution (1) to 100 volumes.
(3) 0.05% w/v of *pimobendan for system suitability EPCRS*.
(4) Dilute 3 volumes of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4.0 mm) packed with *end-capped octadecylsilyl silica gel* (5 µm) (Nucleosil RP C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 0.7 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelengths of 328 nm and 312 nm.
(f) Inject 10 µL of each solution.
(g) Allow the chromatography to proceed for 1.5 times the retention time of pimobendan.

MOBILE PHASE

34 volumes of *acetonitrile* and 66 volumes of 0.05M *diammonium hydrogen orthophosphate*, previously adjusted to pH 5.5 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions the retention times relative to pimobendan (retention time about 5 minutes) are; impurity A, about 0.6 and impurity B, about 0.7.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3) at 328 nm, the resolution between impurity A and impurity B is at least 1.5.

LIMITS

At 312 nm In the chromatogram obtained with solution (1), the area of any peak corresponding to impurity B is not greater than half the area of the principal peak due to impurity B in the chromatogram obtained with solution (2) (0.5%).

At 328 nm In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than twice the area of the principal peak A in the chromatogram obtained with solution (2) (2.0%);

the area of any other *secondary peak* is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of any other *secondary peaks* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.3%).

Uniformity of content

Capsules containing less than 2 mg and/or less than 2% w/w of Pimobendan comply with the requirements stated under Capsules using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Add one capsule to 5 mL of *water* and shake until the capsule has dispersed. Add 15 mL of *methanol* and mix with the aid of ultrasound. Allow to cool and dilute to 25 mL with *methanol*. Centrifuge and dilute a quantity of the supernatant liquid with *methanol*, if necessary, to produce a solution expected to contain 0.005% w/v of Pimobendan.
(2) 0.005% w/v of *pimobendan BPCRS* in *methanol*.
(3) 0.05% w/v of *pimobendan for system suitability EPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used with a wavelength of 328 nm.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the resolution between impurity A and impurity B is at least 1.5.

DETERMINATION OF CONTENT

Calculate the total content of pimobendan, $C_{19}H_{18}N_4O_2$, in each capsule using the declared content of $C_{19}H_{18}N_4O_2$, in *pimobendan BPCRS*.

ASSAY

For capsules containing the equivalent of less than 2 mg and/or less than 2% w/w of Pimobendan

Use the average of the individual results determined in the test for Uniformity of content.

For capsules containing the equivalent of 2 mg or more and 2% w/w or more of Pimobendan

Weigh and powder the contents of 20 capsules. Carry out the method for liquid chromatography, Appendix III D, using the following solutions in *methanol*.

(1) Disperse a quantity of the mixed capsule contents containing 25 mg of Pimobendan and dilute to 100 mL. Further dilute 1 volume to 5 volumes.
(2) 0.005% w/v of *pimobendan BPCRS*.
(3) 0.015% w/v of *pimobendan for system suitability EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used with a wavelength of 328 nm.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between impurity A and impurity B is at least 1.5.

DETERMINATION OF CONTENT

Calculate the total content of $C_{19}H_{18}N_4O_2$, in the capsules using the declared content of $C_{19}H_{18}N_4O_2$, in *pimobendan BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurity A and B listed under Pimobendan.