EAG/Panel/Working Party	Medicinal Chemicals 2
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Notes: New Veterinary monograph If limits are too restrictive, please provide batch/stability data to demonstrate that an increase is required.	

Pimobendan Chewable Tablets

Pimobendan Preparations

Action and use
Inhibitor of phosphodiesterase type III; calcium sensitizer.

DEFINITION

Pimobendan Chewable Tablets contain Pimobendan.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of pimobendan, $C_{19}H_{18}N_4O_2$
93.0 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 powdered tablets containing 10 mg of Pimobendan with 10 mL of *methanol*. Filter and use the filtrate.

(2) 0.1% 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 under *ultraviolet light (254nm).*

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.

For tablets containing 2.5 mg or less of Pimobendan

TEST CONDITIONS

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

(b) Use 500 mL of 2.93 g *sodium chloride* and 2.04 mL *hydrochloric acid* 37% dissolved in 750 mL *water*, adjusted to pH 1.8 and made up to 1000 mL with *water*, 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 further medium solution if necessary, to produce a solution expected to contain 0.00025% w/v of Pimobendan.

(2) 0.00025% w/v of *pimobendan BPCRS* in *methanol*.

For tablets containing more than 2.5 mg of Pimobendan

TEST CONDITIONS

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

(b) Use 900 mL of 2.93 g *sodium chloride* and 2.04 mL *hydrochloric acid* 37% dissolved in 750 mL *water*, adjusted to pH 1.8 and made up to 1000 mL with *water*, 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 further medium solution if necessary, to produce a solution expected to contain 0.0005% w/v of Pimobendan.

(2) 0.0005% w/v of *pimobendan BPCRS* in *methanol*.

(3) 0.00015% w/v of *pimobendan for system suitability EPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (5 cm × 3 mm) packed with *octadecylsilyl silica gel for chromatography* (1.7 µm).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.4 mL per minute.

(d) Use a column temperature of 45°.

(e) Use a detection wavelength of 290 nm.

(f) Inject 2 µL of each solution.

MOBILE PHASE

28 volumes of *acetonitrile* and 70 volumes of a solution of 0.60 g *sodium dihydrogen orthophosphate* and 0.811 g *sodium chloride* in 900 ml of *water*, adjusted to pH 7.2 with *sodium hydroxide* and diluted with *water* to 1000 ml.

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.

(1) Disperse a quantity powdered tablets containing 5 mg of Pimobendan in 25 mL of *methanol* and mix until the tablets have completely dissolved.

(2) Dilute 1 volume of solution (1) to 100 volumes with solution A.

(3) 0.0015% w/v of *pimobendan for system suitability EPCRS* in *methanol*.

(4) Dilute 3 volumes of solution (2) to 10 volumes with *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (5 cm × 3 mm) packed with *octadecylsilyl silica gel for chromatography* (1.7 µm).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 0.35 mL per minute.

(d) Use a column temperature of 45°.

(e) Use a detection wavelength of 290 nm.

(f) Inject 2 µL of each solution.

MOBILE PHASE

Mobile phase A 70 volumes of a solution of 0.60 g *sodium dihydrogen orthophosphate* and 0.811 g *sodium chloride* in 900 ml of *water*, adjusted to pH 7.2 with *sodium hydroxide* and diluted with *water* to 1000 ml

Mobile phase B 28 volumes of *acetonitrile.*

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0.0	80	20	isocratic
0.0 – 4.5	80→38	20→62	linear gradient
4.5 – 5.2	38→80	62→20	linear gradient
5.2 – 6.0	80	20	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retention times relative to pimobendan (retention time about 3.5 minutes) are; impurity A, about 0.4 and impurity B, about 0.9.

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 2.

LIMITS

In the chromatogram obtained with solution (1) use the chromatogram obtained with solution (3) to identify the peaks due to impurities A and 1.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A or B is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

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

the sum of the area of all *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2.0%).

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

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

(1) Disperse a quantity of the powdered tablets containing 5 mg of Pimobendan in 100 mL of *methanol* and mix until complete dissolution

(2) 0.005% w/v of *pimobendan BPCRS* in *methanol.*

(3) 0.0015% w/v of *pimobendan for system suitability EPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

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 2.0.

DETERMINATION OF CONTENT

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

ASSAY

For tablets containing 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 tablets containing 2 mg or more and 2% w/w or more of Pimobendan

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Disperse a quantity of the powdered tablets containing 5 mg of Pimobendan in 100 mL of *methanol* and mix until complete dissolution

(2) 0.005% w/v of *pimobendan BPCRS* in *methanol.*

(3) 0.0015% w/v of *pimobendan for system suitability EPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between impurity A and impurity 1 is at least 4.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{19}H_{18}N_4O_2$ in the tablets 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 listed under Pimobendan and:

1. 3-hydroxy-6-[2-(4-hydroxyphenyl)-1*H*-benzimidazol-5-yl]-5-methyl-pyridazine.