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_{23}H_{37}N_{3}O_{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 (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).

**A.** 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 octadecylsilica 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 C₁₀H₁₄N₂O₂ in the medium from the chromatograms obtained and using the declared content of C₁₀H₁₄N₂O₂ in pimobendan BPCS.

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 EPCS 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°C.
(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.

<table>
<thead>
<tr>
<th>Time (Minutes)</th>
<th>Mobile phase A (% v/v)</th>
<th>Mobile phase B (% v/v)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>80</td>
<td>20</td>
<td>isocratic</td>
</tr>
<tr>
<td>0.0 – 4.5</td>
<td>80→38</td>
<td>20→62</td>
<td>linear gradient</td>
</tr>
<tr>
<td>4.5 – 5.2</td>
<td>38→80</td>
<td>62→20</td>
<td>linear gradient</td>
</tr>
<tr>
<td>5.2 – 6.0</td>
<td>80</td>
<td>20</td>
<td>re-equilibration</td>
</tr>
</tbody>
</table>

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) (0.5%).

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 BPCS in methanol.
3) 0.0015% w/v of pimobendan for system suitability EPCS 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.

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 BPCS in methanol.
3) 0.0015% w/v of pimobendan for system suitability EPCS 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_{4}O_{2} in the tablets using the declared content of C_{10}H_{16}N_{4}O_{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)-1H-benzimidazol-5-yl]-5-methyl-pyridazine.