Phenoxympethylpenicillin Tablets

General Notices

Details for the public consultation of this monograph are as follows:

<table>
<thead>
<tr>
<th>EAG/Panel/Working Party</th>
<th>EAG ABS - Antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contact Details</td>
<td><a href="mailto:stephen.maddocks@mhra.gov.uk">stephen.maddocks@mhra.gov.uk</a></td>
</tr>
<tr>
<td></td>
<td><a href="mailto:peter.crowley@mhra.gov.uk">peter.crowley@mhra.gov.uk</a></td>
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<tr>
<td>Deadline for Comment</td>
<td>31st March 2019</td>
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<tr>
<td>Target Publication Date (subject to change)</td>
<td>BP 2020</td>
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<tr>
<td>Notes:</td>
<td>Revision to monograph</td>
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<tr>
<td></td>
<td>Addition of Related Substances procedure and specific impurity limits</td>
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<tr>
<td></td>
<td>Revision to Assay procedure.</td>
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</tbody>
</table>

Action and use

Penicillin antibacterial.

DEFINITION

Phenoxympethylpenicillin Tablets contain Phenoxympethylpenicillin Potassium.

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

Content of phenoxympethylpenicillin, C₁₆H₁₈N₂O₅S, calculated as the sum of the contents of phenoxympethylpenicillin and 4-hydroxyphenoxympethylpenicillin

92.5 to 107.5% of the stated amount of phenoxympethylpenicillin.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing the equivalent of 80 mg of phenoxympethylpenicillin with water, dilute to 250 mL with water and filter. The light absorption of the filtrate, Appendix II B, exhibits maxima at 268 nm and 274 nm and a minimum at 272 nm.

B. Shake a quantity of the powdered tablets containing the equivalent of 10 mg of phenoxympethylpenicillin with 10 mL of water, filter and add 0.5 mL of neutral red solution. Add sufficient 0.01M sodium hydroxide to produce a permanent orange colour and then add 1.0 mL of penicillinase solution. The colour changes rapidly to red.

C. Ignite 0.5 g of the powdered tablets, add 5 mL of 2M hydrochloric acid, boil, cool and filter. The filtrate yields reaction B characteristic of potassium salts, Appendix VI.
**TESTS**

**Dissolution**

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

**TEST CONDITIONS**

(a) Use Apparatus 1, rotating the basket at 100 revolutions per minute.
(b) Use 900 mL of a 0.68% w/v solution of *potassium dihydrogen orthophosphate*, adjusted to pH 6.8 by the addition of 1M *sodium hydroxide*, at a temperature of 37°, as the medium.

**PROCEDURE**

(1) After 45 minutes withdraw a 10 mL sample of the medium and measure the absorbance of the filtered sample, suitably diluted with the dissolution medium if necessary, at the maximum at 268 nm, *Appendix II B*, using dissolution medium in the reference cell.
(2) Measure the absorbance of a suitable solution of *phenoxymethylpenicillin potassium BPCRS* in dissolution medium using dissolution medium in the reference cell.

**DETERMINATION OF CONTENT**

Calculate the total content of phenoxymethylpenicillin, C₁₆H₁₈N₂O₅S, in the medium from the absorbances obtained and from the declared content of C₁₆H₁₈N₂O₅S in *phenoxymethylpenicillin potassium BPCRS*.

**Related substances**

Carry out the method for liquid chromatography *Appendix III D*, using the following solutions in solution A. Prepare immediately before use.

Solution A To 250 volumes of 0.2 M *Potassium dihydrogen phosphate* add 500 volumes of *water*, adjust to pH 6.5 with a 0.84% w/v solution of *sodium hydroxide*, dilute to 1000 volumes with *water*.

(1) Dissolve a quantity of the powdered tablets containing the equivalent of 0.4% w/v of phenoxymethylpenicillin.
(2) Dilute 1 volume of solution (1) to 100 volumes.
(3) 0.4% w.v *phenoxymethylpenicillin for system suitability EPCRS*.
(4) Dilute 1 volume of solution (2) to 5 volumes.

**CHROMATOGRAPHIC CONDITIONS**

(a) Use a stainless steel column (15 cm x 4.6 mm) packed with *end capped octadecylsilyl silica gel for chromatography* (3 µm) (YMC-Pack Pro is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use a column temperature of 50 °C.
(e) Use a detection wavelength of 254 nm.
(f) Inject 20 µL of each solution.

**MOBILE PHASE**

Mobile Phase A 10 volumes of phosphate buffer solution pH 3.4, 30 volumes of methanol, and 60 volumes of water.
Mobile phase B 5 volumes of phosphate buffer solution pH 3.4, 35 volumes of water, and 60 volumes of methanol.

<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>0-2</td>
<td>85</td>
<td>15</td>
<td>isocratic</td>
</tr>
<tr>
<td>2-5</td>
<td>85→70</td>
<td>15→30</td>
<td>linear gradient</td>
</tr>
<tr>
<td>5-17</td>
<td>70→0</td>
<td>30→100</td>
<td>linear gradient</td>
</tr>
<tr>
<td>17-22</td>
<td>0</td>
<td>100</td>
<td>isocratic</td>
</tr>
<tr>
<td>22-23</td>
<td>0→85</td>
<td>100→15</td>
<td>linear gradient</td>
</tr>
<tr>
<td>23-35</td>
<td>85</td>
<td>15</td>
<td>re-equilibration</td>
</tr>
</tbody>
</table>

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to phenoxymethylpenicillin (retention time, about 11 minutes) are: impurity B, about 0.3; impurity D, about 0.4; impurity E, about 0.55 and 0.61; impurity F, about 0.88 and 0.95

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the resolution between the peaks due to the epimers of impurity F is at least 3.0

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to impurities B, D, E, and F using the chromatogram supplied with phenoxymethylpenicillin for system suitability EPCRS, and the chromatogram obtained with solution (3).

Multiply the area of any peak corresponding to impurity B, D, and E by the following correction factors respectively: 0.6, 1.7, and 1.3.

In the chromatogram obtained with solution (1):

the sum of the areas of any peaks corresponding to the isomers of impurity E or the epimers impurity F is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0% of each);

the area of any peak corresponding to impurity B is not greater than 0.3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any peak corresponding to impurity D is not greater than 4 times the area of the principal peak in the chromatogram obtained with solution (2) (4.0%);

the area of any other secondary peak is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (0.2%);

the sum of the areas of all the secondary peaks, other than impurity D, is not greater than 4 times the area of the principal peak in the chromatogram obtained with solution (2) (4.0%).

Disregard any peak with an area less than 0.75 times the area of the principal peak in the chromatogram obtained with solution (4) (0.15%).
ASSAY

Weigh and powder 20 tablets. Carry out the method for liquid chromatography, Appendix III D, using the following solutions in solution A prepared immediately before use.

Solution A: To 250 volumes of 0.2 M potassium dihydrogen phosphate add 500 volumes of water, adjust to pH 6.5 with a 0.84% w/v solution of sodium hydroxide, and dilute to 1000 volumes with water.

(1) Dissolve a quantity of the powdered tablets containing the equivalent of 0.1% w/v of phenoxymethylpenicillin.

CHROMATOGRAPHIC CONDITIONS

Use the chromatographic conditions described under Related substances.

DETERMINATION OF CONTENT

Calculate the content of C_{16}H_{18}N_{2}O_{5}S in the tablets using the declared content of C_{16}H_{18}N_{2}O_{5}S in phenoxymethylpenicillin potassium BPCRS.

Calculate the sum of the percentage contents of phenoxymethylpenicillin and 4-hydroxyphenoxymethylpenicillin (impurity D)

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of phenoxymethylpenicillin.