Status: Effectivity information can only be shown for content published to the website.

Update information can only be shown for content published to the website.

Phenoxymethylpenicillin Tablets

General Notices

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

EAG/Panel/Working Party	EAG ABS - Antibiotics
Contact Details	stephen.maddocks@mhra.gov.uk peter.crowley@mhra.gov.uk
Deadline for Comment	31st March 2019
Target Publication Date (subject to change)	BP 2020
Notes:	Revision to monograph Addition of Related Substances procedure and specific impurity limits Revision to Assay procedure.

Action and use

Penicillin antibacterial.

DEFINITION

Phenoxymethylpenicillin Tablets contain Phenoxymethylpenicillin Potassium.

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

Content of phenoxymethylpenicillin, $C_{16}H_{18}N_2O_5S$, calculated as the sum of the contents of phenoxymethylpenicillin and 4-hydroxyphenoxymethylpenicillin

92.5 to 107.5% of the stated amount of phenoxymethylpenicillin.

IDENTIFICATION

A. Shake a quantity of the powdered tablets containing the equivalent of 80 mg of phenoxymethylpenicillin 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 phenoxymethylpenicillin 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, $C_{16}H_{18}N_2O_5S$, in the medium from the absorbances obtained and from the declared content of $C_{16}H_{18}N_2O_5S$ 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 dihydrogren 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 e*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 temparature of 50 °
(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.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-2	85	15	isocratic
2-5	85→70	15→30	linear gradient
5-17	70→0	30→100	linear gradient
17-22	0	100	isocratic
22-23	0→85	100→15	linear gradient
23-35	85	15	re-equillibration

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.
(1) Dissolve a quantity of the powdered tablets containing the equivalent of 0.1% w/v of phenoxymethylpenicillin. (2) 0.11% w/v of *phenoxymethylpenicillin potassium BPCRS*

CHROMATOGRAPHIC CONDITIONS

Use the chromatographic conditions described under Related substances

DETERMINATION OF CONTENT

Calculate the content of $C_{16}H_{18}N_2O_5S$ in the tablets using the declared content of $C_{16}H_{18}N_2O_5S$ 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.