British Pharmacopoeia Commission Secretariat
MHRA, 10 South Colonnade
Canary Wharf, London
E14 4PU, United Kingdom
pharmacopoeia.com

Date: 25 January 2019

TO WHOM IT MAY CONCERN

PHENOBARBITAL INJECTION BP 2019

RELATED SUBSTANCES IMPURITY LIMITS

It has come to our attention that the impurity limits specified in the Related substances test for Phenobarbital Injection in the BP 2019 will be revised at the earliest opportunity. It has come to our attention that the monograph does not account for two additional impurities (2-phenylbutanoic acid and (2-phenylbutanoyl)urea). The following limits are to be specified in the Related substances test in the next publication of the monograph:

2-phenylbutanoic acid = 1.5%
(2-phenylbutanoyl)urea = 2.0%

There have also been some minor editorial/technical corrections to the text. The Medicinal Chemicals 3 Expert Advisory Group has approved the amendments and the revised monograph is due to be published in the BP2020. The full revised procedures can be found on the following page.

Please accept this as a notice of intent to amend the monograph on behalf of the British Pharmacopoeia Commission. This letter is for information only and does not represent a legally-enforceable standard. The revised monograph will be published in a future edition of the British Pharmacopoeia - the current target publication is the BP 2020, which will come into force on 1st January 2020.

If you have any questions concerning this letter, please do not hesitate to contact the British Pharmacopoeia Secretariat (BPCOM@mhra.gov.uk).

Yours faithfully,

MR JAMES POUND
Secretary & Scientific Director
Email: BPCOM@mhra.gov.uk

Phenobarbital Injection

General Notices

Action and use

Barbiturate.

DEFINITION

Phenobarbital Injection is a sterile solution containing Phenobarbital Sodium in a suitable vehicle.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of phenobarbital sodium, $C_{12}H_{11}N_2NaO_3$

95.0 to 105.0% w/v.

IDENTIFICATION

To a quantity of the injection containing 1 g of Phenobarbital Sodium, add 15 mL of *water*, make slightly acidic with 1 M *sulfuric acid*, filter and retain the residue. Wash the residue with *water* and dry at 105°. The *infrared absorption spectrum* of the residue Appendix II A, is concordant with the reference spectrum of phenobarbital *(RS 270)*.

TESTS

Alkalinity

pH, 10.0 to 11.0, Appendix V L.

Related substances

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

(1) Dilute a quantity of the injection containing 100 mg of Phenobarbital in 100 mL of the mobile phase.
(2) Dilute 1 volume of solution (1) to 10 volumes with the mobile phase. Dilute 1 volume of the resulting solution to 50 volumes with the mobile phase.
(3) 0.0005% w/v each of *phenobarbital impurity A EPCRS* and *phenobarbital impurity B EPCRS*.
(4) 0.0015% w/v of *2-phenylbutanoic acid* in the mobile phase.
(5) 0.002% w/v of *(2-Phenylbutanoyl)urea* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb S5 ODS 2 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.
(e) Use a detection wavelength of 254 nm.
(f) Inject 20 µL of each solution.
(g) Allow the chromatography to proceed for three times the retention time of phenobarbital.

MOBILE PHASE

25 volumes of *acetonitrile* and 75 volumes of a solution of 0.66% w/v of *sodium acetate* in *water*, adjusted to pH 4.5 using *glacial acetic acid*.

When the chromatograms are recorded under the prescribed conditions the retention times relative to phenobarbital (retention time, about 9 minutes) are: impurity A, about 0.4; impurity B, about 0.5; 2-phenylbutanoic acid, about 2.0; (2-phenylbutanoyl)urea, about 2.30.

SYSTEM SUITABILITY

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

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to 2-phenylbutanoic acid is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (1.5%);

the area of any peak corresponding to (2-phenylbutanoyl)urea (impurity E) is not greater than the area of the principal peak in the chromatogram obtained with solution (5) (2.0%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of *secondary peaks*, excluding any peaks corresponding to 2-phenylbutanoic acid or (2-phenylbutanoyl)urea, is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

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

(1) Dilute a weighed quantity of the injection containing 100 mg of Phenobarbital in 100 mL of the mobile phase. Dilute 1 volume of the resulting solution to 10 volumes with the mobile phase.
(2) 0.01% w/v of *phenobarbital BPCRS* in the mobile phase.
(3) A solution of 0.0005% w/v of *phenobarbital impurity A EPCRS* and 0.0005% w/v of *phenobarbital impurity B EPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

Use the chromatographic conditions described under the test for Related substances.

SYSTEM SUITABILITY

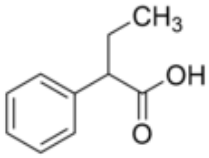
The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and impurity B is at least 1.5.

DETERMINATION OF CONTENT

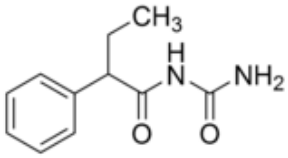
Calculate the content of $C_{12}H_{11}N_2NaO_3$ in the injection from the chromatograms obtained using the declared content of $C_{12}H_{11}N_2NaO_3$ in *phenobarbital BPCRS*. Each mg of *phenobarbital BPCRS* is equivalent to 1.095 mg of Phenobarbital sodium.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Phenobarbital Sodium and those listed below:



1. 2-phenylbutanoic acid



E. (2*RS*)-*N*-carbamimidoyl-2-phenylbutanamide; (2-Phenylbutanoyl)urea