British Pharmacopoeia

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TO WHOM IT MAY CONCERN

Phenobarbital Injection – Related substances impurity limits

The impurity limits specified in the Related substances test for Phenobarbital Injection 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 letter of intent on behalf of the British Pharmacopoeia Commission.

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

Yours sincerely,

Mr James Pound
Secretary & Scientific Director

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Phenobarbital Injection

Phenobarbital Preparations

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% of the stated amount.

IDENTIFICATION

To a quantity of the injection containing 1 g of Phenobarbital Sodium, add 15 mL of *water*, make slightly acidic with 1M *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 to 100 mL with 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) A solution of 0.0005% w/v of *phenobarbital impurity A EPCRS*, 0.0005% w/v of *phenobarbital impurity B EPCRS*, 0.0005% w/v of *(2-phenylbutanoyl)urea* and 0.0015% w/v of *2-phenylbutanoic acid* 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 3 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

Identify the peaks due to impurity A, impurity B, 2-phenylbutanoic acid and (2-phenylbutanoyl)urea using the chromatogram obtained with solution (3) and multiply the area of any peak due to 2-phenylbutanoic acid by a correction factor of 3.2.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to 2-phenylbutanoic acid is not greater than 7.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%);

the area of any peak corresponding to (2-phenylbutanoyl)urea is not greater than ten times the area of the principal peak in the chromatogram obtained with solution (2) (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 0.5 times 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 to 100 mL with 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*, 0.0005% w/v of *phenobarbital impurity B EPCRS*, 0.0005% w/v of *(2-phenylbutanoyl)urea* and

0.0015% w/v of *2-phenylbutanoic acid* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

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

SYSTEM SUITABILITY

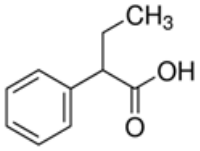
The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and impurity B is at least 1.5.

DETERMINATION OF CONTENT

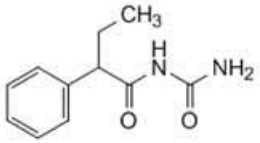
Determine the *weight per mL* of the injection, Appendix V G, and calculate the content of $C_{12}H_{11}N_2NaO_3$, weight in volume, using the declared content of $C_{12}H_{12}N_2O_3$ in *phenobarbital BPCRS*. Each mg of *phenobarbital BPCRS* is equivalent to 1.095 mg of Phenobarbital sodium.

IMPURITIES

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



1. 2-phenylbutanoic acid



2. (2-phenylbutanoyl)urea