Edition: BP 2025 (Ph. Eur. 11.6 update)

Proguanil Tablets

General Notices

Action and use

Antiprotozoal (malaria).

DEFINITION

Proguanil Tablets contain Proguanil Hydrochloride.

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

Content of proguanil hydrochloride, $C_{11}H_{16}ClN_5,HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. To a quantity of the powdered tablets containing 0.2 g of Proguanil Hydrochloride add 25 mL of *methanol*, shake for 10 minutes, filter, evaporate the filtrate to dryness and dry the residue at 105°. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of proguanil hydrochloride (*RS 294*).
B. Boil a quantity of the powdered tablets containing 0.5 g of Proguanil Hydrochloride with 5 mL of 2M *hydrochloric acid*, cool and filter. To the filtrate add a slight excess of 5M *sodium hydroxide*, extract with 30 mL of *ether*, evaporate the ether and dry the residue at 105°. The *melting point* of the residue is about 131°, Appendix V A.

TESTS

4-Chloroaniline

To a quantity of the powdered tablets containing 0.1 g of Proguanil Hydrochloride add 5 mL of *ethanol* (*96%*) and shake for 10 minutes. Add 2.5 mL of 2M *hydrochloric acid* and 15 mL of *water*, mix and filter through a moistened filter paper, washing the filter with 5 mL of *water*. Cool the filtrate to 5°, add 1 mL of 0.05M *sodium nitrite*, allow to stand at 5° for 5 minutes, add 2 mL of a 5% w/v solution of *ammonium sulfamate* and allow to stand for 10 minutes. Add 2 mL of a 0.1% w/v solution of N-*(1-naphthyl)ethylenediamine dihydrochloride*, dilute to 50 mL with *water* and allow to stand for 30 minutes. Any magenta colour produced is not more intense than that obtained by treating in the same manner and at the same time 20 mL of a solution containing 1.25 µg per mL of *4-chloroaniline* (250 ppm).

Related substances

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

(1) Add 50 mL of *methanol* to a quantity of the powdered tablets containing 0.1 g of Proguanil Hydrochloride, shake for 10 minutes, dilute to 100 mL with *methanol*, mix, filter and dilute 5 mL of the filtrate to 50 mL with the mobile phase.
(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase.

(3) 1 volume of a 0.05% w/v solution of *1-(2,5-dichlorophenyl)-5-isopropylbiguanide hydrochloride BPCRS* in *methanol* with 9 volumes of a 0.010% w/v solution of *proguanil hydrochloride BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 5 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use a column temperature of 40°.
(e) Use a detection wavelength of 254 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

1.89 g of *sodium hexanesulfonate* in a mixture of 500 mL of *methanol*, 500 mL of *water* and 5 mL of *glacial acetic acid*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated peaks due to proguanil hydrochloride and 1-(2,5-dichlorophenyl)-5-isopropylbiguanide hydrochloride.

LIMITS

In the chromatogram obtained with solution (1):

the sum of the areas of any *secondary peaks* in the chromatogram obtained with solution (1) is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%).

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 2, rotating the paddle at 50 revolutions per minute.
(b) Use 900 mL of 0.2M *hydrochloric acid* containing 0.2% w/v of *sodium chloride*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 withdraw a sample of 10 mL of the medium, filter and dilute 2 mL of the filtrate to 10 mL with dissolution medium. Measure the *absorbance* of this solution, Appendix II B, at 242 nm using dissolution medium in the reference cell.
(2) Measure the *absorbance* of a 0.001% w/v solution of *proguanil hydrochloride BPCRS* in dissolution medium using dissolution medium in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of proguanil hydrochloride, $C_{11}H_{16}ClN_5$,HCl, in the medium from the absorbances obtained and from the declared content of $C_{11}H_{16}ClN_5$,HCl in *proguanil hydrochloride BPCRS*.

ASSAY

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

(1) Weigh and powder 20 tablets, add 50 mL of *methanol* to a quantity of the powdered tablets containing 0.1 g of Proguanil Hydrochloride, shake for 10 minutes, dilute to 100 mL with *methanol*, mix and filter. To 5 mL of the filtrate add sufficient *methanol* to produce 50 mL and dilute 10 mL of the resulting solution to 50 mL with the mobile phase.
(2) 0.002% w/v of *proguanil hydrochloride BPCRS* in the mobile phase.
(3) 1 volume of a 0.05% w/v solution of *1-(2,5-dichlorophenyl)-5-isopropylbiguanide hydrochloride BPCRS* in *methanol* with 9 volumes of a 0.010% w/v solution of *proguanil hydrochloride BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated peaks due to proguanil hydrochloride and 1-(2,5-dichlorophenyl)-5-isopropylbiguanide hydrochloride.

DETERMINATION OF CONTENT

Calculate the content of $C_{11}H_{16}ClN_5,HCl$ in the tablets using the declared content of $C_{11}H_{16}ClN_5,HCl$ in *proguanil hydrochloride BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed in the monograph for Proguanil Hydrochloride.