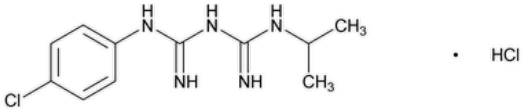
https://trungtamthuoc.com/

Status: Currently Official on 16-Feb-2025
Official Date: Official as of 01-May-2020
Document Type: USP Monographs
DocId: GUID-35985294-FCCA-439B-A275-32C23C836885_2_en-US
DOI: https://doi.org/10.31003/USPNF_M69950_02_01
DOI Ref: f72r1

© 2025 USPC
Do not distribute

Proguanil Hydrochloride



$C_{11}H_{16}ClN_5 \cdot HCl$ 290.19

Biguanide, 1-(4-chlorophenyl)-5-isopropyl, hydrochloride;

1-(*p*-Chlorophenyl)-5-isopropylbiguanide hydrochloride CAS RN®: 637-32-1; UNII: R71Y86M0WT.

DEFINITION

Proguanil Hydrochloride contains NLT 98.5% and NMT 101.0% of proguanil hydrochloride ($C_{11}H_{16}ClN_5 \cdot HCl$), calculated on the dried basis.

IDENTIFICATION

Change to read:

• **A.** ▲**Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*: 197K**▲ (CN 1-May-2020)

• **B.** **Identification Tests—General, *Chloride*⟨191⟩:** Meets the requirements

ASSAY

• **Procedure**

Solution A: 0.65 g/L of 1-pentanesulfonic acid sodium salt and 7.0 g/L of sodium perchlorate in water. Adjust with 1% trifluoroacetic acid to a pH of 3.0.

Solution B: 0.65 g/L of 1-pentanesulfonic acid sodium salt and 7.0 g/L of sodium perchlorate in a mixture of methanol, acetonitrile, and water (400:400:200). Add 4 mL of 1% trifluoroacetic acid to 1 L of this solution.

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	75	25
20	40	60
25	75	25
35	75	25

Diluent: Acetonitrile, methanol, and water (200:200:600)

Standard solution: 0.2 mg/mL of USP Proguanil Hydrochloride RS in *Diluent*

Sample solution: 0.2 mg/mL of Proguanil Hydrochloride in *Diluent*

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 235 nm

Column: 4.6-mm × 7.5-cm; 3.5-µm packing L7

Column temperature: 40°

Flow rate: 1.5 mL/min

OFFICIAL

www.webofpharma.com

https://trungtamthuoc.com/

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 0.73%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of proguanil hydrochloride ($C_{11}H_{16}ClN_5 \cdot HCl$) in the portion of Proguanil Hydrochloride taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of proguanil from the *Sample solution*

r_S = peak response of proguanil from the *Standard solution*

C_S = concentration of USP Proguanil Hydrochloride RS in the *Standard solution* (mg/mL)

C_U = concentration of Proguanil Hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: 98.5%–101.0% on the dried basis

IMPURITIES

• **Residue on Ignition ⟨281⟩:** NMT 0.1%

• **Limit of Chloroaniline**

Solution A: 3.45 g/L solution of sodium nitrite

Solution B: 50 g/L solution of ammonium sulfamate

Solution C: 1 mg/mL of naphthylethylenediamine dihydrochloride in water. Prepare immediately before use.

Standard solution: 1.25 mg/L solution of chloroaniline

Sample solution: Dissolve 100 mg in 1 mL of 2 N hydrochloric acid, and dilute with water to 20 mL.

Analysis: Cool the *Sample solution* to 5°. Add 1 mL of *Solution A*, and allow to stand at 5° for 5 min. Add 2 mL of *Solution B*, and allow to stand for 10 min. Add 2 mL of *Solution C*, dilute with water to 50 mL, and allow to stand for 30 min.

Acceptance criteria: Any red color produced is not more intense than that of a standard prepared at the same time and in the same manner, using 20 mL of *Standard solution* (250 ppm).

• **Organic Impurities, Procedure 1**

[Note—On the basis of the synthetic route, perform either *Procedure 1* or *Procedure 2*. *Procedure 2* is recommended when proguanil related compound A, proguanil related compound E, proguanil related compound F, and proguanil related compound G (see *Table 3*) may be present.]

Mobile phase: Dissolve 3.78 g of sodium hexanesulfonate in a mixture of 1200 mL of methanol, 800 mL of water, and 10 mL of glacial acetic acid.

Identification solution: 0.5 µg/mL of USP Proguanil Related Compound C RS in *Mobile phase*

System suitability stock solution: 0.5 µg/mL of USP Proguanil Related Compound D RS in *Mobile phase*

System suitability solution: Dilute 1 mL of the *Standard stock solution* with *Mobile phase* to 200 mL. To 1 mL of the resulting solution, add 1 mL of *System suitability stock solution*.

Standard stock solution: 0.1 mg/mL of USP Proguanil Hydrochloride RS in *Mobile phase*

Standard solution: 0.2 µg/mL of USP Proguanil Hydrochloride RS from the *Standard stock solution* in *Mobile phase*

Sample solution: 0.1 mg/mL of Proguanil Hydrochloride in *Mobile phase*

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 230 and 254 nm

Column: 4.6-mm × 12.5-cm; 5-µm packing L1, or 4.6-mm × 15-cm; 5-µm packing L1

Flow rate: 1 mL/min

Injection volume: 20 µL

Run time: At least 5 times the retention time of the proguanil peak at both wavelengths

System suitability

Samples: *System suitability solution* and *Standard solution*

Suitability requirements

OFFICIAL

https://trungtamthuoc.com/

Resolution: NLT 5 between proguanil related compound D and proguanil, *System suitability solution* at 230 nm

Relative standard deviation: NMT 10.0%, *Standard solution* at 230 nm

Analysis

Samples: *Identification solution*, *System suitability stock solution*, *Standard solution*, and *Sample solution*

[NOTE—The relative retention times for proguanil related compound D, proguanil, and proguanil related compound C are about 0.46, 1.0, and 2.5, respectively.]

Identify the components based on their relative retention times, and measure the responses for the major peaks.

Calculate the percentage of proguanil related compound C and proguanil related compound D, as detected at 230 nm, in the portion of Proguanil Hydrochloride taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of proguanil related compound C or proguanil related compound D from the *Sample solution*

r_S = peak response of proguanil from the *Standard solution*

C_S = concentration of USP Proguanil Hydrochloride RS in the *Standard solution* (mg/mL)

C_U = concentration of Proguanil Hydrochloride in the *Sample solution* (mg/mL)

Calculate the percentage of any other impurity, as detected at 230 nm, in the portion of Proguanil Hydrochloride taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of each impurity at 230 nm from the *Sample solution*

r_S = peak response of proguanil at 230 nm from the *Standard solution*

C_S = concentration of USP Proguanil Hydrochloride RS in the *Standard solution* (mg/mL)

C_U = concentration of Proguanil Hydrochloride in the *Sample solution* (mg/mL)

Calculate the percentage of any other impurity, as detected at 254 nm, in the portion of Proguanil Hydrochloride taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of each impurity at 254 nm from the *Sample solution*

r_S = peak response of proguanil at 254 nm from the *Standard solution*

C_S = concentration of USP Proguanil Hydrochloride RS in the *Standard solution* (mg/mL)

C_U = concentration of Proguanil Hydrochloride in the *Sample solution* (mg/mL)

Calculate the percentage of total impurities as the sum of the calculated percentage contents of known and unknown impurities, considering each peak at the wavelength at which the peak shows the higher value.

Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Proguanil related compound D[a]	0.46	0.2
Proguanil	1.0	—
Proguanil related compound C[b]	2.5	0.2
Any other impurity[c]	—	0.1

OFFICIAL
www.webofpharma.com

https://trungtamthuoc.com/

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Total impurities	—	0.5

[a] 1,5-Diisopropylbiguanide or 1,5-Bis(1-methylethyl)biguanide.

[b] 1,5-Bis(4-chlorophenyl)biguanide.

[c] Disregard any peak below 0.05%.

- **Organic Impurities, Procedure 2**

Solution A, Solution B, Mobile phase, and **Diluent:** Proceed as directed in the *Assay*.

Standard stock solution: 0.2 mg/mL each of USP Proguanil Related Compound A RS, USP Proguanil Related Compound C RS, USP Proguanil Related Compound D RS, USP Proguanil Related Compound E RS, USP Proguanil Related Compound F RS, and USP Proguanil Related Compound G RS in *Diluent*

Standard solution: 0.2 µg/mL of USP Proguanil Hydrochloride RS and 0.2 µg/mL each of USP Proguanil Related Compound A RS, USP Proguanil Related Compound C RS, USP Proguanil Related Compound D RS, USP Proguanil Related Compound E RS, USP Proguanil Related Compound F RS, and USP Proguanil Related Compound G RS in *Diluent* from the *Standard stock solution*

System suitability solution: 0.2 mg/mL of USP Proguanil Hydrochloride RS and 2 µg/mL each of USP Proguanil Related Compound A RS, USP Proguanil Related Compound C RS, USP Proguanil Related Compound D RS, USP Proguanil Related Compound E RS, USP Proguanil Related Compound F RS, and USP Proguanil Related Compound G RS in *Diluent* from the *Standard stock solution*

Sample solution: 0.2 mg/mL of Proguanil Hydrochloride in *Diluent*

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 235 nm

Column: 4.6-mm × 7.5-cm; 3.5-µm packing L7

Column temperature: 40°

Flow rate: 1.5 mL/min

Injection volume: 20 µL

System suitability

Sample: *System suitability solution*

Suitability requirements

Resolution: NLT 2.0 between proguanil and proguanil related compound G

Tailing factor: NMT 2.0 for proguanil

Relative standard deviation: NMT 2.0% for the proguanil peak

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each proguanil related compound and any other impurity in the portion of Proguanil Hydrochloride taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of the proguanil related compound or any other impurity from the *Sample solution*

r_S = peak response of the corresponding proguanil related compound or proguanil (for calculating any other impurity) from the *Standard solution*

C_S = concentration of the corresponding proguanil related compound or proguanil hydrochloride (for calculating any other impurity) in the *Standard solution* (mg/mL)

C_U = concentration of Proguanil Hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: See *Table 3*.

Table 3

OFFICIAL

www.webofpharma.com

https://trungtamthuoc.com/

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Proguanil related compound A[a]	0.11	0.1
Proguanil related compound D[b]	0.34	0.1
Proguanil related compound E[c]	0.51	0.1
Proguanil	1.00	—
Proguanil related compound G[d]	1.05	0.1
Proguanil related compound F[e]	1.38	0.1
Proguanil related compound C[f]	1.49	0.1
Any other impurity	—	0.10
Total impurities	—	0.5

[a] 1-Cyano-3-isopropylguanidine.

[b] 1,5-Diisopropylbiguanide or 1,5-Bis(1-methylethyl) biguanide.

[c] 1-(4-Chlorophenyl)-3-cyanoguanidine.

[d] 1-(3-Chlorophenyl)-5-isopropylbiguanide.

[e] 1-(3,4-Dichlorophenyl)-5-isopropylbiguanide.

[f] 1,5-Bis(4-chlorophenyl)biguanide.

OFFICIAL

SPECIFIC TESTS

• **Acidity or Alkalinity**

Sample: 400 mg

Analysis: Add 0.4 mL of methyl red–methylene blue TS to 35 mL of water maintained at 60°–65°. Neutralize with either 0.01 N sodium hydroxide or 0.01 N hydrochloric acid to a gray color. Add the *Sample*, and stir until completely dissolved.

Acceptance criteria: The solution is gray or green. NMT 0.2 mL of 0.01 N hydrochloric acid is required to change the color of the solution to reddish-violet.

• **Loss on Drying** ⟨731⟩

Analysis: Dry a sample at 105° for 2 h.

Acceptance criteria: NMT 0.5%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in well-closed, light-resistant containers, and store at room temperature.

• **Labeling:** If a test for *Organic Impurities* other than *Procedure 1* is used, then the labeling states with which *Organic Impurities* test the article complies.

• **USP Reference Standards** ⟨11⟩

USP Proguanil Hydrochloride RS

USP Proguanil Related Compound A RS

1-Cyano-3-isopropylguanidine.

$C_5H_{10}N_4$ 126.16

USP Proguanil Related Compound C RS

1,5-Bis(4-chlorophenyl)biguanide.

$C_{14}H_{13}Cl_2N_5$ 322.19

USP Proguanil Related Compound D RS

1,5-Bis(1-methylethyl)biguanide or
1,5-Diisopropylbiguanide.

$C_8H_{19}N_5$ 185.27

USP Proguanil Related Compound E RS

1-(4-Chlorophenyl)-3-cyanoguanidine.

www.webofpharma.com

https://trungtamthuoc.com/

$C_8H_7ClN_4$ 194.62

USP Proguanil Related Compound F RS

1-(3,4-Dichlorophenyl)-5-isopropylbiguanide.

$C_{11}H_{15}Cl_2N_5$ 288.18

USP Proguanil Related Compound G RS

1-(3-Chlorophenyl)-5-isopropylbiguanide.

$C_{11}H_{16}ClN_5$ 253.73

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
PROGUANIL HYDROCHLORIDE	Documentary Standards Support	SM12020 Small Molecules 1
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM12020 Small Molecules 1

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. PF 39(4)

Current DocID: GUID-35985294-FCCA-439B-A275-32C23C836885_2_en-US

DOI: https://doi.org/10.31003/USPNF_M69950_02_01

DOI ref: f72r1

OFFICIAL