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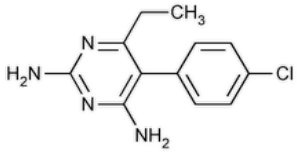
Pyrimethamine

Change to read:



$C_{12}H_{13}ClN_4$ 248.71

2,4-Pyrimidinediamine, 5-(4-chlorophenyl)-6-ethyl-.

2,4-Diamino-5-(▲4▲ (USP 1-May-2024) -chlorophenyl)-6-ethylpyrimidine CAS RN®: 58-14-0; UNII: Z3614QOX8W.

Change to read:

DEFINITION

Pyrimethamine contains ▲NLT 98.0% and NMT 102.0%▲ (USP 1-May-2024) of pyrimethamine ($C_{12}H_{13}ClN_4$) calculated on the dried basis.

IDENTIFICATION

Change to read:

- **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** ▲197A or▲ (USP 1-May-2024) 197K
- **B. Identification Tests—General ⟨191⟩, *Chemical Identification Tests, Chloride***

  Sample solution: Mix about 100 mg of Pyrimethamine with 500 mg of anhydrous sodium carbonate, and ignite the mixture. Cool, add 5 mL of hot water, heat for 5 min on a steam bath, filter, and neutralize the filtrate with nitric acid.

  Acceptance criteria: Meets the requirements
- **C.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

Change to read:

- **Procedure**

  Solution A: Add 1 mL of phosphoric acid to water and dilute with water to 1000 mL.

  Mobile phase: Acetonitrile and *Solution A* (17:83)

  Standard solution: 0.02 mg/mL of USP Pyrimethamine RS in *Solution A*

  Sample solution: 0.02 mg/mL of Pyrimethamine in *Solution A*

  Chromatographic system

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

  Mode: LC

  Detector: UV 210 nm

  Column: 2.0-mm × 10-cm; 3-µm packing L11

  Flow rate: 0.3 mL/min

  Injection volume: 5 µL

  System suitability

  Sample: *Standard solution*

  Suitability requirements

  ▲▲ (USP 1-May-2024)

  Tailing factor: NMT 1.8

  Relative standard deviation: NMT ▲0.73%▲ (USP 1-May-2024)

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of pyrimethamine ($C_{12}H_{13}ClN_4$) in the portion of Pyrimethamine taken:

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

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

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

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

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

Acceptance criteria: ▲98.0%–102.0%▲ (USP 1-May-2024) on the dried basis

IMPURITIES

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

Delete the following:

▲• **Ordinary Impurities ⟨466⟩**▲ (USP 1-May-2024)

Add the following:

▲• **Organic Impurities**

Solution A: 2.72 g/L of potassium phosphate monobasic in water. Adjust with 25% ammonium hydroxide to a pH of 8.0.

Solution B: Acetonitrile

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	65	35
6	65	35
20	40	60
30	55	45
35	65	35
40	65	35

Diluent: *Solution A* and *Solution B* (50:50)

Sensitivity solution: 0.0005 mg/mL of USP Pyrimethamine RS in *Diluent*

Standard solution: 0.001 mg/mL of USP Pyrimethamine RS in *Diluent*. Sonicate to dissolve.

Sample solution: 1 mg/mL of Pyrimethamine in *Diluent*. Sonicate to dissolve.

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: 10 µL

System suitability

Samples: *Sensitivity solution* and *Standard solution*

[Note—The relative retention times in *Table 2* are provided as information that could aid in peak assignment.]

Table 2

Name	Relative Retention Time
Chlorophenyl oxopentanenitrile[a]	0.56
3-Deschloro metoprine[b]	0.75
Pyrimethamine	1.0
p-Chlorobenzyl nitrile[c]	1.4
Chlorophenyl ketal analog[d]	2.1

[a] 2-(4-Clorophenyl)-3-oxopentanenitrile.

[b] 5-(4-Chlorophenyl)-6-methylpyrimidine-2,4-diamine.

[c] 2-(4-Chlorophenyl)acetonitrile.

[d] 2-(4-Chlorophenyl)-2-(2-ethyl-1,3-dioxolan-2-yl)acetonitrile.

Suitability requirements

Relative standard deviation: NMT 5.0%, *Standard solution*

Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Pyrimethamine taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

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

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

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

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

F = relative response factor (see *Table 3*)

Acceptance criteria: See *Table 3*. The reporting threshold is 0.05%.

Table 3

Name	Relative Response Factor	Acceptance Criteria, NMT (%)
Chlorophenyl oxopentanenitrile	0.44	0.10
3-Deschloro metoprine	1.1	0.10
p-Chlorobenzyl nitrile	0.44	0.10
Chlorophenyl ketal analog	0.21	0.10
Any unspecified impurity	1.0	0.10
Total impurities	—	0.50

▲ (USP 1-May-2024)

SPECIFIC TESTS

Delete the following:

▲• **Melting Range or Temperature** ⟨741⟩▲ (USP 1-May-2024)

• **Loss on Drying** ⟨731⟩

Analysis: Dry it at 105° for 4 h.

Acceptance criteria: NMT 0.5%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight, light-resistant containers.

• **USP Reference Standards** ⟨11⟩

USP Pyrimethamine RS

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

Topic/Question	Contact	Expert Committee
PYRIMETHAMINE	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:
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