

BRIEFING

**Chloroquine Sulfate.** This monograph was posted on the USP Website as a draft USP Non-US Monograph on April 30, 2010 and has been available for public comment for more than 90 days. The MD-SM1 Expert Committee has reviewed the comments received and has approved the monograph as an Authorized USP Non-US Monograph. The following is a summary of comments and the responses:

**Comment 1:** It is proposed to change the relative retention time for monoethyl chloroquine in *Impurity Table 1* from 0.42 to 0.52 to be consistent with the original data submitted.  
*Response:* Comment incorporated.

**Comment 2:** It is proposed to add *Description and Solubility* in the briefing to be consistent with more recent USP Web monographs for drug substances.  
*Response:* Comment incorporated.

The HPLC procedure in the test for *Organic Impurities* is based on analyses performed with the Phenomenex Luna C18 brand of L1 column. The typical retention times for the chloroquine peak is about 15 min.

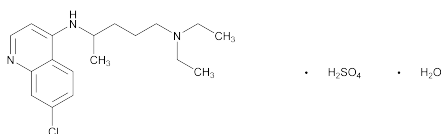
**Description and Solubility:** White or almost white, crystalline powder. Freely soluble in water and in methanol; very slightly soluble in alcohol; practically insoluble in ether.

(SM1: B. Davani.)

Correspondence Number—C83887

## Chloroquine Sulfate

v.1 Authorized January 1, 2011



$C_{18}H_{26}ClN_3 \cdot H_2SO_4 \cdot H_2O$  435.97  
*N*<sup>4</sup>-(7-Chloroquinolin-4-yl)-*N*<sup>1</sup>,*N*<sup>1</sup>-diethylpentane-1,4-diamine sulfate, monohydrate [132-73-0].

### DEFINITION

Chloroquine Sulfate contains NLT 98.5% and NMT 101.0% of  $C_{18}H_{26}ClN_3 \cdot H_2SO_4$ , calculated on the anhydrous basis.

### IDENTIFICATION

**A. INFRARED ABSORPTION** (197S)

**Sample solution:** Dissolve 100 mg in 10 mL of water, add 2 mL of dilute sodium hydroxide, and extract with two 20-mL portions of methylene chloride. Combine the organic layers, wash with water, and dry with anhydrous sodium sulfate. Evaporate to dryness, and dissolve the residue in 2 mL of methylene chloride.

**B. ULTRAVIOLET ABSORPTION** (197U)

**Sample solution:** 10 µg/mL in water  
**Wavelength range:** 210–370 nm

**C. IDENTIFICATION TESTS—GENERAL, Sulfate** (191)

### ASSAY

**PROCEDURE**

**Sample:** 8 mg/mL in glacial acetic acid

**Analysis:** Titrate with 0.1 N perchloric acid VS, and determine the endpoint potentiometrically (see *Titrimetry* (541)). Each mL

of 0.1 N perchloric acid is equivalent to 41.8 mg of  $C_{18}H_{26}ClN_3 \cdot H_2SO_4$

**Acceptance criteria:** 98.5%–101.0% on the anhydrous basis

### IMPURITIES

**Inorganic Impurities**

- **RESIDUE ON IGNITION** (281): NMT 0.1%
- **HEAVY METALS, Method I** (231): NMT 20 ppm

**Organic Impurities**

**PROCEDURE**

**Solution A:** 0.4% triethylamine in methanol

**Solution B:** 1.41 g/L of anhydrous dibasic sodium phosphate in water. Adjust with 10% phosphoric acid solution to a pH of 3.0.

**Mobile phase:** *Solution A* and *Solution B* (7:3)

**Standard solution:** 2.0 µg/mL of USP Chloroquine Sulfate RS, 2.0 µg/mL of USP Phenol RS, and 2.0 µg/mL of USP Chloroquine Related Compound A RS in *Mobile phase*

**Sample solution:** 2 mg/mL of Chloroquine Sulfate in *Mobile phase*

**Chromatographic system**

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

**Mode:** LC

**Detector:** UV 260 nm

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

**Flow rate:** 1 mL/min

**Injection size:** 20 µL

**System suitability**

**Sample:** *Standard solution*

**Suitability requirements**

**Resolution:** NLT 2.0 between the chloroquine sulfate and chloroquine related compound A peaks

**Relative standard deviation:** NMT 5.0% for chloroquine sulfate, phenol, and chloroquine related compound A

**Analysis**

**Samples:** *Standard solution* and *Sample solution*

[NOTE—The relative retention times are listed in *Impurity Table 1*.]

Calculate the percentage of chloroquine sulfate related compound A and phenol in the portion of Chloroquine Sulfate taken:

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

$r_U$  = peak response of chloroquine related compound A or phenol from the *Sample solution*

$r_S$  = peak response of chloroquine related compound A or phenol from the *Standard solution*

$C_S$  = concentration of USP Chloroquine Related Compound A RS or USP Phenol RS in the *Standard solution* (mg/mL)

$C_U$  = concentration of Chloroquine Sulfate in the *Sample solution* (mg/mL)

Calculate the percentage of monoethyl chloroquine, 5-chloroquine isomer, and any other individual impurity in the portion of Chloroquine Sulfate taken:

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

$r_U$  = peak response of monoethyl chloroquine, 5-chloroquine isomer, or any other individual impurity in the *Sample solution*

$r_S$  = peak response of chloroquine from the *Standard solution*

$C_S$  = concentration of USP Chloroquine Sulfate RS from the *Standard solution* (mg/mL)

$C_U$  = concentration of Chloroquine Sulfate in the *Sample solution* (mg/mL)

F = relative response factor (see *Impurity Table 1*)

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### Acceptance criteria

Individual impurities: See *Impurity Table 1*.

Total impurities: NMT 1.0%

**Impurity Table 1**

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Phenol	0.19	—	0.10
Monoethyl chloroquine <sup>a</sup>	0.52	1.1	0.50
Chloroquine related compound A <sup>b</sup>	0.73	—	0.10
Chloroquine	1.0	—	—
5-Chloroquine isomer <sup>c</sup>	1.46	0.72	0.10
Any other individual impurity	—	1.0	0.10

<sup>a</sup> 7-Chloro-4-[[4-(ethylamino)-1-methylbutyl]amino]quinoline.

<sup>b</sup> 4,7-Dichloroquinoline.

<sup>c</sup> *N*-(5-Chloroquinolin-4-yl)-*N*<sup>1</sup>,*N*<sup>1</sup>-diethylpentane-1,4-diamine.

### SPECIFIC TESTS

- **WATER DETERMINATION, Method Ia (921):** 3.0%–5.0%
- **PH (791):** 4.0–5.0, 2.0 g in 25 mL of carbon dioxide-free water

### ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers. Store at controlled room temperature.
- **USP REFERENCE STANDARDS (11)**
  - USP Chloroquine Sulfate RS
  - USP Phenol RS
  - USP Chloroquine Related Compound A RS
  - 4,7-Dichloroquinoline.
  - C<sub>9</sub>H<sub>5</sub>Cl<sub>2</sub>N 198.05