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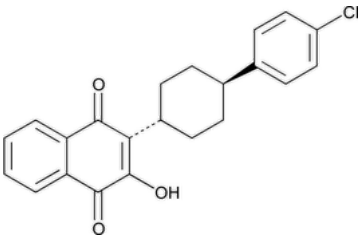
Atovaquone



$C_{22}H_{19}ClO_3$ 366.84

1,4-Naphthalenedione, 2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-, *trans*-;

2-[*trans*-4-(*p*-Chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone CAS RN®: 95233-18-4; UNII: Y883P1Z2LT.

DEFINITION

Atovaquone contains NLT 97.5% and NMT 101.5% of atovaquone ($C_{22}H_{19}ClO_3$), calculated on the anhydrous and organic solvent-free basis.

IDENTIFICATION

• **A.** **Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*: 197M**

• **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

• **Procedure**

Mobile phase: Acetonitrile, methanol, water, and phosphoric acid (525:175:300:5)

Diluent: Acetonitrile and water (80:20)

System suitability solution: 0.25 mg/mL of USP Atovaquone RS and 0.02 mg/mL of USP Atovaquone Related Compound A RS in *Diluent*. Store in a low-actinic glass container.

Standard solution: 0.25 mg/mL of USP Atovaquone RS in *Diluent*

Sample solution: 0.25 mg/mL of Atovaquone in *Diluent*. Use a low-actinic volumetric flask.

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm × 25-cm; packing L1

Flow rate: 3 mL/min

Injection volume: 20 µL

System suitability

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

[Note—The relative retention times for atovaquone related compound A and atovaquone are about 0.85 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 4 between atovaquone related compound A and atovaquone, *System suitability solution*

Column efficiency: NLT 9000 theoretical plates, *Standard solution*

Tailing factor: NMT 1.5, *Standard solution*

Relative standard deviation: NMT 2%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of atovaquone ($C_{22}H_{19}ClO_3$) in the portion of Atovaquone taken:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

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

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

Acceptance criteria: 97.5%–101.5% on the anhydrous and organic solvent-free basis

IMPURITIES

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

Change to read:

• **▲Organic Impurities**

Mobile phase, Diluent, System suitability solution, Standard solution, Sample solution, Chromatographic system and **System suitability:** Proceed as directed in the *Assay*.

Analysis

Sample: *Sample solution*

Calculate the percentage of atovaquone related compounds in the portion of Atovaquone taken:▲ (ERR 1-Jun-2023)

$$\text{Result} = (r_U/r_T) \times 100$$

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

r_T = sum of all the peak responses from the *Sample solution*

Acceptance criteria: See *Table 1*.

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Indene isomer[a]	0.63	0.5
Atovaquone related compound A	0.85	1.0
Didehydroatovaquone[b]	0.89	0.3
Atovaquone	1.0	—
O-Methyl atovaquone[c]	1.8	0.5
Any other individual, unidentified impurity	—	0.2
Sum of all other individual impurities	—	1.0
Total impurities	—	1.5

[a] *trans*-2-[4-(4-Chlorophenyl)cyclohexyl]-1-oxo-1*H*-indene-3-carboxylic acid.

[b] (*RS*)-2-[4-(4-Chlorophenyl)cyclohex-3-enyl]-3-hydroxy-1,4-naphthoquinone.

[c] *trans*-2-[4-(4-Chlorophenyl)cyclohexyl]-3-methoxy-1,4-naphthoquinone.

SPECIFIC TESTS

• **Water Determination, *Method I*⟨921⟩:** NMT 1.0%

ADDITIONAL REQUIREMENTS

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

• **USP Reference Standards ⟨11⟩**

USP Atovaquone RS

USP Atovaquone Related Compound A RS

cis-2-[4-(4-Chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone.

$C_{22}H_{19}ClO_3$ 366.84

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

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