

BRIEFING

Lumefantrine. This monograph has been posted on the USP SALMOUS Standards Web page for review and public comment for more than 90 days. The MD-AA Expert Committee reviewed the following comment and approved the monograph as an Authorized USP SALMOUS Standard.

Comment: It is proposed to delete the *Description and solubility* section, because it is not part of the requirement for the monograph.

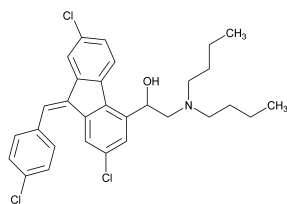
Response: Comment accepted.

The HPLC procedures used in the *Assay* and the test for *Related compounds*, although different, are both based on analyses performed with the Nucleosil-100 C18 (5- μ m) brand of L1 column. The typical retention times for lumefantrine in the *Assay* and *Related compounds* methods are about 11 to 12 minutes.

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Lumefantrine

v.1 Authorized February 1, 2009



C₃₀H₃₂Cl₃NO 528.94
(±)-2,7-Dichloro-9-[(Z)-p-chlorobenzylidene]- α [(dibutylamino)methyl]-fluorene-4-methanol [82186-77-4].

» Lumefantrine contains not less than 98.0 percent and not more than 102.0 percent of C₃₀H₃₂Cl₃NO.

Packaging and storage—Preserve in well-closed containers. Store at room temperature.

USP Reference standards (11)—*USP Lumefantrine RS*. *USP Lumefantrine Related Compound A RS*. *USP Lumefantrine Related Compound B RS*.

Identification—

A: *Infrared Absorption* (197K).

B: The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation*, as obtained in the *Assay*.

Residue on ignition (281): not more than 0.1%.

Heavy metals, Method II (231): 0.001%.

Related compounds—

Ion-pairing solution, *Solution A*, and *Solution B*—Proceed as directed in the *Assay*.

Solution C—Prepare a mixture of 1-propanol, acetonitrile, and water (4 : 1 : 1).

Mobile phase—Use variable mixtures of *Solution A*, *Solution B*, and *Solution C* as directed for *Chromatographic system*. Make adjustments if necessary (see *System Suitability* under *Chromatography* (621)).

System suitability solution—Dissolve in acetonitrile accurately weighed quantities of USP Lumefantrine RS, USP Lumefantrine Related Compound A RS, and USP Lumefantrine Related

Compound B RS to obtain a solution having concentrations of about 0.26 mg per mL, 0.02 mg per mL, and 0.02 mg per mL, respectively.

Test solution—Dissolve a quantity of Lumefantrine in acetonitrile to obtain a solution having a known concentration of about 0.26 mg per mL.

Chromatographic system (see *Chromatography* (621))—The liquid chromatograph is equipped with a 265-nm detector and a 4.0-mm \times 12.5-cm column that contains 5- μ m packing L1. The flow rate is about 2.0 mL per minute. The chromatograph is programmed as follows.

Time (min)	Solution A (%)	Solution B (%)	Solution C (%)	Elution
0–14	25	75	0	isocratic
14–19	25→0	75→100	0	linear gradient
19–20	0	100→80	0→20	linear gradient
20–26	0	80	20	isocratic
26–27	0	80→30	20→70	linear gradient
27–50	0	30	70	isocratic
50–51	0→25	30→75	70→0	linear gradient
51–56	25	75	0	re-equilibration

Chromatograph the *System suitability solution*, and record the peak responses as directed for *Procedure*. Identify the components on the basis of their relative retention times, as given in *Table 2*: the resolution, *R*, between lumefantrine and lumefantrine related compound A is not less than 0.5; and the relative standard deviation for replicate injections is not more than 2.0% for the lumefantrine peak.

Procedure—Inject a volume (about 20 μ L) of the *Test solution* into the chromatograph, record the chromatogram, and measure the peak responses. Identify the impurities using the relative retention times specified in *Table 1*.

Table 1

Compound	Relative Retention Time	Limit (%)
Lumefantrine related compound A ¹	0.8	0.1
Lumefantrine related compound B ² (stereoisomer A)	3.7	0.1
Lumefantrine related compound B ² (stereoisomer B)	4.0	0.3
Lumefantrine	1.0	—
Any individual unknown impurity	—	0.10
Total impurities	—	0.3

¹ (*RS,Z*)-2-(Dibutylamino)-2-(2,7-dichloro-9-(4-chlorobenzylidene)-9H-fluoren-4-yl)ethanol [C₃₀H₃₂Cl₃NO, 528.94].

² Lumefantrine related compound B is a mixture of stereoisomers A and B, with the following tentative names:

(1*S*,3*R*,5*R*)-1,3-bis((*EZ*)-2,7-Dichloro-9-(4-chlorobenzylidene)-9H-fluoren-4-yl)-2,6-dioxabicyclo[3.1.0]hexane [C₄₄H₃₄Cl₆O₂, 797.4];

2-((*EZ*)-2,6-Dichloro-9-(4-chlorobenzylidene)-9H-fluoren-4-yl)-3'-((*EZ*)-2,7-dichloro-9-(4-chlorobenzylidene)-9H-fluoren-4-yl)-2,2'-bioxirane [C₄₄H₃₄Cl₆O₂, 797.4].

Calculate the percentage of each impurity in the portion of Lumefantrine taken by the formula:

$$100(r_i/r_s)$$

in which *r_i* is the peak area for each individual impurity and *r_s* is the sum of all responses of all the peaks. Disregard any peak less than 0.05%.

Assay—

Ion-pairing solution—Prepare a mixture of 5.65 g of sodium 1-hexanesulfonate and 2.75 g of monobasic sodium phosphate in 800 mL of water. Adjust with phosphoric acid to a pH of 2.3, dilute with water to 1000.0 mL, and filter.

Solution A—Prepare a mixture of water, acetonitrile, *Ion-pairing solution*, and 1-propanol (50 : 25 : 20 : 5).

Solution B—Prepare a mixture of acetonitrile, *Ion-pairing solution*, water, and 1-propanol (65 : 20 : 10 : 5).

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Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system*. Make adjustments if necessary (see *System Suitability* under *Chromatography* (621)).

System suitability solution—Dissolve in acetonitrile accurately weighed quantities of USP Lumefantrine RS, USP Lumefantrine Related Compound A RS, and USP Lumefantrine Related Compound B RS to obtain a solution having concentrations of 0.26 mg per mL, 0.02 mg per mL, and 0.02 mg per mL, respectively.

Standard preparation—Dissolve an accurately weighed quantity of USP Lumefantrine RS in acetonitrile to obtain a solution having a known concentration of about 0.26 mg per mL.

Assay preparation—Transfer about 13 mg of Lumefantrine, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with acetonitrile to volume, and mix.

Chromatographic system (see *Chromatography* (621))—The liquid chromatograph is equipped with a 265-nm detector and a 4.0-mm × 12.5-cm column that contains 5-μm packing L1. The flow rate is about 2.0 mL per minute. The chromatograph is programmed as follows.

Time (min)	<i>Solution A</i> (%)	<i>Solution B</i> (%)	Elution
0–14	25	75	isocratic
14–19	25→0	75→100	linear gradient
19–20	0	100	isocratic

Time (min)	<i>Solution A</i> (%)	<i>Solution B</i> (%)	Elution
20–21	0→25	100→75	linear gradient
21–26	25	75	re-equilibration

Chromatograph the *System suitability solution*, and record the peak responses as directed for *Procedure*; the relative retention times are about 0.8 for lumefantrine related compound A and 1.0 for lumefantrine; the resolution, *R*, between the lumefantrine and lumefantrine related compound A peaks is not less than 0.5; and the relative standard deviation for replicate injections is not more than 1.0%.

Procedure—Separately inject equal volumes (about 10 μL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the lumefantrine peak. Calculate the percentage of C₃₀H₃₂Cl₃NO in the portion of Lumefantrine taken by the formula:

$$100(C_s/C_U)(r_U/r_s)$$

in which *C_s* and *C_U* are the concentrations, in mg per mL, of lumefantrine in the *Standard preparation* and the *Assay preparation*, respectively; and *r_U* and *r_s* are the peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively.