Orphenadrine Citrate Extended-Release Tablets

Type of Posting	Revision Bulletin
Posting Date	29–Jul–2016
Official Date	01–Aug–2016
Expert Committee	Chemical Medicines Monographs 4
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015-2020 Council of Experts, the Chemical Medicines Monographs 4 Expert Committee has revised the Orphenadrine Citrate Extended-Release Tablets.

The purpose for the revision is to:

- Add *Dissolution Test* 3 to accommodate a drug product which was approved with different dissolution test conditions and acceptance criteria than the existing dissolution tests.

- Revise the acceptance criteria of the any individual unspecified degradation product in the *Organic Impurities* section from NMT 0.10% to NMT 0.2% based on the specification for an FDA approved drug product.

- Correct the calculation for the concentration (*Ci*) of orphenadrine citrate in *Dissolution Test* 2.

The Orphenadrine Citrate Extended-Release Tablets Revision Bulletin supersedes the currently official monograph. The Revision Bulletin will be incorporated in the *First Supplement to USP 40–NF 35*.

Should you have any questions, please contact Gerald Hsu, Ph.D., Senior Scientific Liaison, (240-221-3097 or gdh@usp.org).

Orphenadrine Citrate Extended-Release Tablets

DEFINITION

Orphenadrine Citrate Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of orphenadrine citrate ($C_{18}H_{23}NO \cdot C_6H_8O_7$).

IDENTIFICATION

- **A.** 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**

Buffer: ▲5.8▲*USP39* g/L of monobasic ammonium phosphate. Adjust with phosphoric acid to a pH of 3.2. ▲▲*USP39*

Mobile phase: Acetonitrile and *Buffer* (40:60)

▲System suitability solution: 0.1 mg/mL of USP Orphenadrine Citrate RS and 0.01 mg/mL each of USP Orphenadrine Related Compound B RS and USP Orphenadrine Related Compound C RS, in *Mobile phase* ▲*USP39*

Standard solution: 0.1 mg/mL of USP Orphenadrine Citrate RS

Sample stock solution: Nominally 0.5 mg/mL of orphenadrine citrate prepared as follows. Transfer a quantity of powder equivalent to NLT 100 mg of orphenadrine citrate, from finely powdered Tablets (NLT 20), to a suitable volumetric flask. Add 50% of the flask volume of *Mobile phase*. Sonicate for 5 min and shake for 15 min. Dilute with *Mobile phase* to volume. Pass through a suitable filter.

Sample solution: Nominally 0.1 mg/mL of orphenadrine citrate in *Mobile phase* from the *Sample stock solution*

Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 225 nm
Column: 3.9-mm × 30-cm; ▲10-µm▲*USP39* L1 packing
Flow rate: 2 mL/min
Injection volume: 20 µL

System suitability
Samples: ●*System suitability solution* and● (RB 1-Aug-2016) *Standard solution*
Suitability requirements
▲Resolution: NLT 1.2 between orphenadrine and orphenadrine related compound C; NLT 2.0 between orphenadrine citrate and orphenadrine related compound B, ●System suitability solution● (RB 1-Aug-2016)▲*USP39*
Tailing factor: NMT 2.0, ●Standard solution● (RB 1-Aug-2016)
Relative standard deviation: NMT 2.0%, *Standard solution*

Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of orphenadrine citrate ($C_{18}H_{23}NO \cdot C_6H_8O_7$) in the portion of Tablets 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 Orphenadrine Citrate RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of orphenadrine citrate in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

- **DISSOLUTION** ⟨**711**⟩

Test 1
Medium: Water; 900 mL, deaerated
Apparatus 2: 50 rpm
Times: 1, 2, 6, and 12 h
Buffer: ▲5.8▲*USP39* g/L of monobasic ammonium phosphate in water
Mobile phase: Acetonitrile and *Buffer* (40:60). Adjust with phosphoric acid to a pH of 3.2 ± 0.1.
Standard stock solution: 1 mg/mL of USP Orphenadrine Citrate RS in *Mobile phase*. ▲Sonication may be used to promote dissolution.▲*USP39*
Standard solution 0.1 mg/mL of USP Orphenadrine Citrate RS in *Medium* from a suitable volume of *Standard stock solution* and *Medium*
Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size and discard the first few mL of the filtrate.
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 225 nm
Column: 3.9-mm × 30-cm; ▲10-µm▲*USP39* packing L1
Flow rate: 2 mL/min
Injection volume: 20 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.0
Relative standard deviation: NMT 2.0%
Analysis:
Samples: *Standard solution* and *Sample solution*
▲Calculate the concentration (C_i) of orphenadrine citrate ($C_{18}H_{23}NO \cdot C_6H_8O_7$) dissolved in the portion of the sample withdrawn at each time point (*i*) (mg/mL):

$$C_i = (r_U/r_S) \times C_S$$

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of the *Standard solution* (mg/mL)

Calculate the percentage of the labeled amount of orphenadrine citrate ($C_{18}H_{23}NO \cdot C_6H_8O_7$) dissolved at each time point (*i*):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$

$$\text{Result}_2 = \{[C_2 \times (V - V_S)] + (C_1 \times V_S)\} \times (1/L) \times 100$$

$$\text{Result}_3 = \{C_3 \times [V - (2 \times V_S)] + [(C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

$$\text{Result}_4 = \{C_4 \times [V - (3 \times V_S)] + [(C_3 + C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

C_i = concentration of orphenadrine citrate in the portion of the sample withdrawn at time point (*i*) (mg/mL)
V = volume of *Medium*, 900 mL
L = label claim (mg/Tablet)
V_S = volume of the *Sample solution* withdrawn at each time point (mL)▲*USP39*

Tolerances: See *Table 1*.

Table 1

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	1	10–40
2	2	30–50
3	6	50–80
4	12	NLT 80

•The percentages of the labeled amount of orphenadrine citrate ($C_{18}H_{23}NO \cdot C_6H_8O_7$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.• (RB 1-Aug-2016)

Test 2: If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 2*.

Medium: Water; 900 mL
Apparatus 2: 50 rpm
Times: 1, 4, and 12 h
Standard solution: 0.02 mg/mL of USP Orphenadrine Citrate RS in *Medium*
Sample solution: Withdraw 10 mL of the solution under test from each vessel at each specified time point. Replace 10 mL of *Medium* in each vessel. Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size. Transfer 1.0 mL of the filtrate to a 50-mL volumetric flask, and dilute with *Medium* to volume.
Blank: *Medium*
Instrumental conditions
•(See *Ultraviolet-Visible Spectroscopy* ⟨857⟩.)• (RB 1-Aug-2016)
Mode: UV
Analytical wavelength: 210 nm
▲**Analysis**
Samples: *Standard solution* and *Sample solution*
Calculate the concentration (C_i) of orphenadrine citrate ($C_{18}H_{23}NO \cdot C_6H_8O_7$) in the sample withdrawn from the vessel at each time point (*i*):

$$\bullet C_i = (A_U/A_S) \times C_S$$

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of the *Standard solution* (mg/mL)

• (RB 1-Aug-2016)

Calculate the percentage of the labeled amounts (Q_i) of orphenadrine citrate ($C_{18}H_{23}NO \cdot C_6H_8O_7$) dissolved at each time point *(i)*:

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$

$$\text{Result}_2 = [(C_2 \times V) + (C_1 \times V_S)] \times (1/L) \times 100$$

$$\text{Result}_3 = \{(C_3 \times V) + [(C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

C_i = concentration of orphenadrine citrate in the portion of the sample withdrawn at time point (*i*) (mg/mL)
V = volume of *Medium*, 900 mL
L = label claim (mg/Tablet)
V_S = volume of the *Sample solution* withdrawn at each time point (mL)▲*USP39*

Tolerances: See *Table 2*.

Table 2

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	1	10–40
2	4	40–70
3	12	NLT 80

•The percentages of the labeled amount of orphenadrine citrate ($C_{18}H_{23}NO \cdot C_6H_8O_7$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

Test 3: If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 3*.

Solution A: 0.45 M monobasic potassium phosphate prepared as follows. Mix 6.12 g of monobasic potassium phosphate and 12 mL of 10 N sodium hydroxide. Dilute with water to 100 mL.
Acid stage medium: 0.1 N hydrochloric acid; 800 mL
Buffer stage medium: pH 7.5 phosphate buffer (add 100 mL of *Solution A* to the *Acid stage medium* after 1 h); 900 mL
Apparatus 2: 50 rpm
Times: 1 h in *Acid stage medium*; 4 and 10 h in *Buffer stage medium*. The time in the *Buffer stage medium* includes the time in the *Acid stage medium*.
Standard solution: 0.11 mg/mL of USP Orphenadrine Citrate RS in *Acid stage medium*
Sample solution: Pass a portion of the solution under test through a suitable filter.
Blank: *Acid stage medium*
Instrumental conditions
(See *Ultraviolet-Visible Spectroscopy* ⟨857⟩.)
Mode: UV
Analytical wavelength: 232 nm
Cell: 1 cm
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the concentration (C_i) of orphenadrine citrate ($C_{18}H_{23}NO \cdot C_6H_8O_7$) in the sample withdrawn from the vessel at each time point (*i*):

$$C_i = (A_U/A_S) \times C_S$$

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of the *Standard solution* (mg/mL)

Calculate the percentage of the labeled amounts (Q_i) of orphenadrine citrate ($C_{18}H_{23}NO \cdot C_6H_8O_7$) dissolved at each time point *(i)*:

$$\text{Result}_1 = C_1 \times V_A \times (1/L) \times 100$$

$$\text{Result}_2 = \{[C_2 \times (V_B - V_S)] + (C_1 \times V_S)\} \times (1/L) \times 100$$

$$\text{Result}_3 = (\{C_3 \times [V_B - (2 \times V_S)]\} + [(C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

C_i = concentration of orphenadrine citrate in the portion of the sample withdrawn at time point (*i*) (mg/mL)

V_A = volume of *Acid stage medium*, 800 mL
L = label claim (mg/Tablet)
V_B = volume of *Buffer stage medium*, 900 mL
V_S = volume of the *Sample solution* withdrawn at each time point (mL)

Tolerances: See *Table 3*.

Table 3

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	1	40–55
2	4	50–70
3	10	NLT 70

The percentages of the labeled amount of orphenadrine citrate ($C_{18}H_{23}NO \cdot C_6H_8O_7$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.● (RB 1-Aug-2016)

- **Uniformity of Dosage Units** ⟨**905**⟩**:** Meet the requirements

IMPURITIES

Change to read:

- **Organic Impurities**

Buffer, Mobile phase, ▲System suitability solution, ▲*USP39* Sample solution, Chromatographic system, and **▲System suitability:▲*USP39*** Proceed as directed in the *Assay*.

Analysis

Sample: *Sample solution*

Calculate the percentage of each ▲degradation product▲*USP39* in the portion of Tablets taken:

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

r_U = peak response of each ▲degradation product▲*USP39* from the *Sample solution*
r_S = peak response of orphenadrine from the *Sample solution*
F = relative response factor for each ▲degradation product▲*USP39* (see *Table 4*)

Acceptance criteria: See *Table 4*.

▲Table 4

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Citric acid[a]	0.4	—	—
Orphenadrine related compound C	0.9	1.5	0.5
Orphenadrine citrate	1	—	—
Orphenadrine related compound B	1.3	1.3	0.5
2-Methylbenzhydrol[b]	2.1	2.1	0.5
2-Methylbenzophenone[c]	4	1.0	0.5
Any individual unspecified degradation product	—	1.0	●0.2● (RB 1-Aug-2016)
Total degradation products	—	—	1.5

[a] The peak is due to counter ion and is not to be reported or included in total degradation products.
[b] Also known as Phenyl(*o*-tolyl)methanol.
[c] Also known as Phenyl(*o*-tolyl)methanone.

▲*USP39*

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in well-closed, tight, light-resistant containers, and store at controlled room temperature.
- **Labeling:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.

Change to read:

- **USP Reference Standards** ⟨**11**⟩

USP Orphenadrine Citrate RS

USP Orphenadrine Related Compound B RS
N-Ethyl-*N,N*-dimethyl [2-2(methylbenzhydryloxy)ethyl]ammonium chloride;
▲Also known as *N*-Ethyl-*N,N*-dimethyl-2-[phenyl(*o*-tolyl)methoxy]ethanaminium chloride.▲*USP39*
$C_{20}H_{28}ClNO$ 333.90

USP Orphenadrine Related Compound C RS
N-Methyl [2-(2-methylbenzhydryloxy)ethyl]amine hydrochloride;
▲Also known as *N*-Methyl-2-[phenyl(*o*-tolyl)methoxy-]ethanamine hydrochloride.▲*USP39*
$C_{17}H_{22}ClNO$ 291.82