Lamotrigine Extended-Release Tablets

Type of Posting	Revision Bulletin
Posting Date	25–Jan–2019
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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 Lamotrigine Extended-Release Tablets monograph. The purpose for the revision is to add *Dissolution Test 7* to accommodate FDA-approved drug products with different tolerances than the existing dissolution tests.

- *Dissolution Test 7* was validated using a Waters Symmetry C8 brand of L7 column. The typical retention time for lamotrigine is about 3.5 min.

The revision also necessitates a change in the table numbering in the test for *Organic Impurities*.

The Lamotrigine Extended-Release Tablets Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Ren-Hwa Yeh, Senior Scientific Liaison (301-998-6818 or rhy@usp.org).

Lamotrigine Extended-Release Tablets

DEFINITION

Lamotrigine Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of lamotrigine ($C_9H_7Cl_2N_5$).

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

• **PROCEDURE**

Mobile phase: Acetonitrile, water, and trifluoroacetic acid (25: 75: 0.05)

Diluent: Acetonitrile, methanol, and water (10:20:70)

Standard solution: 0.25 mg/mL of USP Lamotrigine RS in *Diluent*. Sonication may be used to aid dissolution.

Sample stock solution: 1.0–3.0 mg/mL of lamotrigine prepared as follows. Transfer NLT 5 Tablets to a suitable volumetric flask containing 10% of the flask volume of acetonitrile. Allow the Tablets to disperse. Add 20% of the flask volume of methanol. Sonicate for 10 min. Add 30% of the flask volume of 0.1 M hydrochloric acid. Sonicate for 25 min or until a fine, even dispersion is obtained. Allow to cool to room temperature. Dilute with 0.1 M hydrochloric acid to volume. Pass a portion of the solution through a nylon filter of 0.45-µm pore size and use the filtrate.

Sample solution: Nominally 0.2–0.3 mg/mL of lamotrigine in 0.1 M hydrochloric acid from a suitable volume of *Sample stock solution*

Chromatographic system

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

Mode: LC

Detector: UV 270 nm

Column: 4.6-mm × 15-cm; 3-µm packing L1

Column temperature: 40°

Flow rate: 1 mL/min

Injection volume: 5 µL

Run time: NLT 8 times the retention time of lamotrigine

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 1.5%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of lamotrigine ($C_9H_7Cl_2N_5$) 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 Lamotrigine RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of lamotrigine in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

• **DISSOLUTION** ⟨711⟩

Test 1

Medium 1: 0.01 M hydrochloric acid; 700 mL

Medium 2: 7.8 g of tribasic sodium phosphate, and 22.5 g of sodium dodecyl sulfate in 1 L of water. This solution has a pH of about 12.

Apparatus 2: 50 rpm with sinkers (see *Dissolution* ⟨711⟩, *Figure 2a*)

Times

For Tablets labeled to contain 25 or 50 mg: 2, 7, 15 h

For Tablets labeled to contain 100, 200, or 250 mg: 2, 5, 12 h

For Tablets labeled to contain 300 mg: 2, 6, 13 h

Procedure: Run the test with *Medium 1* for 2 h. Add 200 mL of *Medium 2*, preheated at 37°. Within 5 min of the addition of *Medium 2*, withdraw the sample for the 2-h time point. Continue the testing by drawing samples at the time points specified in *Table 1*, *Table 2*, or *Table 3*, depending on the label claim.

Diluent: *Medium 1* and *Medium 2* (70:20)

Standard solution: (*L*/900) mg/mL of USP Lamotrigine RS in *Diluent*, where *L* is the label claim in mg/Tablet

Sample solution: Pass a suitable portion of the solution under test through a suitable filter of 0.45-µm pore size. Dilute with *Diluent* if necessary.

Blank: *Diluent*

Instrumental conditions

Mode: UV

Analytical wavelength: 260 nm. [NOTE—Depending on the label claim, cells with suitable path lengths may be used.]

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount (Q_i) of lamotrigine ($C_9H_7Cl_2N_5$) dissolved at each time point *i*:

$$\text{Result} = (A_U/A_S) \times C_S \times V \times D \times (1/L) \times 100$$

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of the *Standard solution* (mg/mL)
V = volume of *Medium*, 900 mL
D = dilution factor if needed
L = label claim (mg/Tablet)

Tolerances

For Tablets with 25- or 50-mg label claim: See *Table 1*.

For Tablets with 100-, 200-, or 250-mg label claim: See *Table 2*.

For Tablets with 300-mg label claim: See *Table 3*.

Table 1

Time Point (*i*)	Time (h)	Amount Dissolved
1	2	NMT 10%
2	7	35%–55%
3	15	NLT 80%

Table 2

Time Point (*i*)	Time (h)	Amount Dissolved	
		100 mg, 200 mg	250 mg
1	2	NMT 10%	NMT 10%
2	5	20%–45%	20%–40%
3	12	NLT 80%	NLT 80%

Table 3

Time Point (*i*)	Time (h)	Amount Dissolved
1	2	NMT 10%
2	6	25%–45%
3	13	NLT 80%

The percentages of the labeled amount of lamotrigine ($C_9H_7Cl_2N_5$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

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

Acid stage medium: 0.01 M hydrochloric acid; 700 mL

Buffer stage stock medium: 2.83 g of sodium phosphate monobasic, 1.72 g of sodium hydroxide, and 22.5 g of sodium dodecyl sulfate in 1 L of water

Buffer stage medium: *Acid stage medium* and *Buffer stage stock medium* (70:20); 900 mL. Adjust with solution A (phosphoric acid in water prepared by diluting 1 mL of phosphoric acid with water to 50 mL) or 0.1 N sodium hydroxide, if necessary, to a pH of 6.8. Record the required volume of solution A or 0.1 N sodium hydroxide for adjustment of pH to 6.8.

Apparatus 2: 50 rpm with stationary tablet basket. See *Figures 1* and *2*.

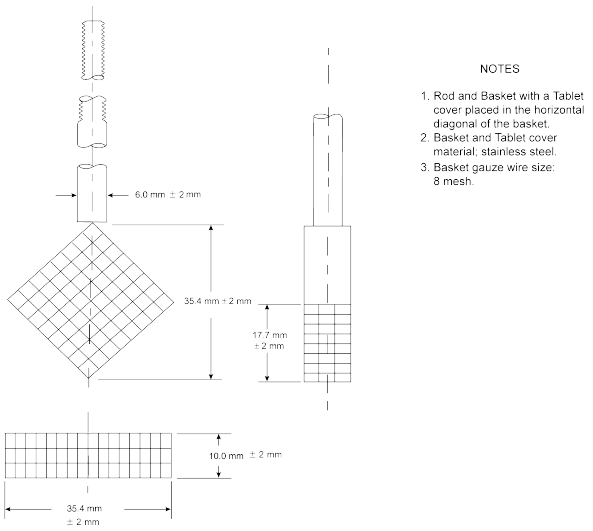

Figure 1. Stationary tablet basket.

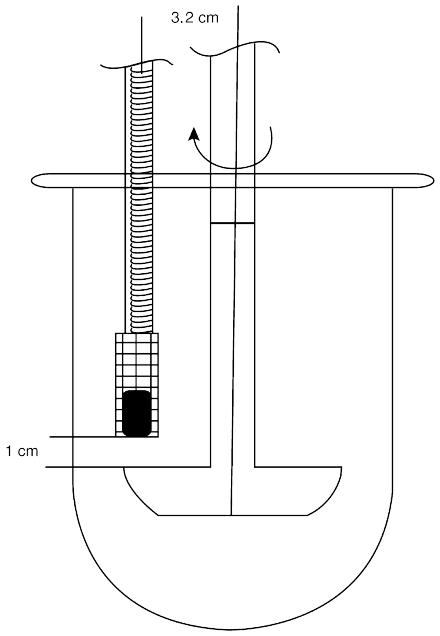

Figure 2. Drug release stationary tablet basket configuration diagram.

Times

For Tablets labeled to contain 25 or 50 mg: 2 h in *Acid stage medium*; 4, 7, 9, and 15 h in *Buffer stage medium*

For Tablets labeled to contain 100, 200, or 300 mg: 2 h in *Acid stage medium*; 3, 5, 7, and 12 h in *Buffer stage medium*

[NOTE—The times in the *Buffer stage medium* include the time in the *Acid stage medium*.]

Procedure: Run the test with *Acid stage medium* for 2 h followed by collecting the *Acid stage medium* sample and replacing it with the same volume of *Acid stage medium*. Add 200 mL of *Buffer stage stock medium* to the above solution. If necessary, add either solution A or 0.1 N sodium hydroxide to the solution to reach a pH of 6.8. Continue the testing by drawing samples at the time points specified in *Table 4* or *Table 5*, depending on the label claim. Replace each of the volumes withdrawn with an equal volume of *Buffer stage medium*.

Buffer: Dissolve 2.76 g of sodium phosphate monobasic in 1 L of water. Add 2 mL of triethylamine and adjust with solution A to a pH of 7.0.

Mobile phase: Methanol and *Buffer* (55:45)

Standard stock solution: 1.4 mg/mL of USP Lamotrigine RS in methanol

Acid stage standard solution: (*L*/900) mg/mL of USP Lamotrigine RS from *Standard stock solution*, in *Acid stage medium*, where *L* is the label claim in mg/Tablet

Buffer stage standard solution: (*L*/900) mg/mL of USP Lamotrigine RS from *Standard stock solution*, in *Buffer stage medium*, where *L* is the label claim in mg/Tablet

Acid stage sample solution: Withdraw a 10.0-mL aliquot, and pass a portion of the solution under test through a suitable filter of 0.45-µm pore size. Replace the 10.0-mL aliquot withdrawn for analysis with a 10.0-mL aliquot of *Acid stage medium*.

Buffer stage sample solution: Withdraw a 10.0-mL aliquot, and pass a portion of the solution under test

through a suitable filter of 0.45-µm pore size. Replace the 10.0-mL aliquot withdrawn for analysis with a 10.0-mL aliquot of *Buffer stage medium*.

Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 270 nm
Column: 4.6-mm × 15-cm; 5-µm packing L7
Flow rate: 1 mL/min
Injection volume
For 25-mg Tablets: 80 µL
For 50-mg Tablets: 40 µL
For 100-mg Tablets: 20 µL
For 200- or 300-mg Tablets: 10 µL
Run time: NLT 1.8 times the retention time of lamotrigine

System suitability
Samples: *Acid stage standard solution* and *Buffer stage standard solution*
Suitability requirements
Tailing factor: NMT 2.0
Relative standard deviation: NMT 2.0%

Analysis
Samples: *Acid stage standard solution*, *Acid stage sample solution*, *Buffer stage standard solution*, and *Buffer stage sample solution*
Calculate the percentage (Q_A) of the labeled amount of lamotrigine ($C_9H_7Cl_2N_5$) dissolved in the *Acid stage medium*:

$$\text{Result}_i = (r_U/r_S) \times C_S \times V_A \times (1/L) \times 100$$

r_U = peak response from the *Acid stage sample solution*
r_S = peak response from the *Acid stage standard solution*
C_S = concentration of USP Lamotrigine RS in the *Acid stage standard solution* (mg/mL)
V_A = volume of the *Acid stage medium*, 700 mL
L = label claim (mg/Tablet)

Calculate the concentration (C_i) of lamotrigine ($C_9H_7Cl_2N_5$) in the sample withdrawn from the vessel at each time point (*i*) during the buffer stage:

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

r_U = peak response from the *Buffer stage sample solution* at time point *i*
r_S = peak response from the *Buffer stage standard solution*
C_S = concentration of USP Lamotrigine RS in the *Buffer stage standard solution* (mg/mL)

Calculate the percentage of the labeled amount of lamotrigine ($C_9H_7Cl_2N_5$) dissolved at each time point (*i*) during the buffer stage:

$$\text{Result}_1 = [C_1 \times V_B \times (1/L) \times 100] + (Q_A \times V_S/V_A)$$
$$\text{Result}_2 = \{[(C_2 \times V_B) + (C_1 \times V_S)] \times (1/L) \times 100\} + (Q_A \times V_S/V_A)$$
$$\text{Result}_3 = (\{(C_3 \times V_B) + [(C_2 + C_1) \times V_S]\} \times (1/L) \times 100) + (Q_A \times V_S/V_A)$$
$$\text{Result}_4 = (\{(C_4 \times V_B) + [(C_3 + C_2 + C_1) \times V_S]\} \times (1/L) \times 100) + (Q_A \times V_S/V_A)$$

C_i = concentration of lamotrigine in the *Buffer stage sample solution* withdrawn at time point *i* (mg/mL)
V_B = volume of the *Buffer stage medium*, 900 mL
L = label claim (mg/Tablet)
Q_A = the percentage of the labeled amount of lamotrigine dissolved in the *Acid stage medium*
V_S = volume of the sample solution withdrawn at each time point (*i*) during the acid stage or buffer stage (mL)
V_A = volume of the *Acid stage medium*, 700 mL

Tolerances
For Tablets labeled to contain 25 or 50 mg: See *Table 4*.
For Tablets labeled to contain 100, 200, or 300 mg: See *Table 5*.

Table 4

Time Point (*i*)	Time (h)	Amount Dissolved
1	2	NMT 10%
2	4	5%–25%
3	7	30%–50%
4	9	50%–70%
5	15	NLT 80%

Table 5

Time Point (*i*)	Time (h)	Amount Dissolved
1	2	NMT 10%
2	3	5%–20%
3	5	25%–50%
4	7	50%–70%
5	12	NLT 80%

The percentages of the labeled amount of lamotrigine ($C_9H_7Cl_2N_5$) 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 it meets USP *Dissolution Test 3*.
Acid stage medium: 0.01 M hydrochloric acid; 700 mL
Buffer stage stock medium: 7.8 g of sodium phosphate tribasic and 22.5 g of sodium dodecyl sulfate in 1 L of water
Buffer stage medium: *Acid stage medium* and *Buffer stage stock medium* (70:20); 900 mL. Adjust with 2 N hydrochloric acid TS or 2 N sodium hydroxide TS, if necessary, to a pH of 6.8.
Apparatus 2: 50 rpm with stationary tablet basket. See *Figures 1* and *2* in *Test 2*.
Times
For Tablets labeled to contain 25, 50, 100, or 200 mg: 2 h in *Acid stage medium*; 4, 7, and 14 h in *Buffer stage medium*
[NOTE—The times in the *Buffer stage medium* include the time in the *Acid stage medium*.]
Procedure: Run the test with *Acid stage medium* for 2 h followed by collecting the *Acid stage medium* sample and replacing it with the same volume of *Acid stage medium*. Add 200 mL of *Buffer stage stock medium* to the above solution. Continue the testing by drawing samples at the time points specified in *Table 6*. Replace each of the volumes withdrawn with an equal volume of the *Buffer stage medium*.

Buffer: Dissolve 2.72 g of potassium phosphate monobasic in 1 L of water and adjust with dilute phosphoric acid to a pH of 3.7.
Mobile phase: Methanol, acetonitrile, and *Buffer* (50:15:35)
Standard stock solution: 0.6 mg/mL of USP Lamotrigine RS in methanol. Sonicate to dissolve as needed.
Acid stage standard solution: 0.036 mg/mL of USP Lamotrigine RS from *Standard stock solution*, in *Acid stage medium*
Buffer stage standard solution: (*L*/900) mg/mL of USP Lamotrigine RS from *Standard stock solution*, in *Buffer stage medium*, where *L* is the label claim in mg/Tablet
Acid stage sample solution: Withdraw a 10.0-mL aliquot and pass a portion of the solution under test through a suitable filter of 0.45-µm pore size, discarding the first 5 mL of the filtrate. Replace the 10.0-mL aliquot withdrawn for analysis with a 10.0-mL aliquot of *Acid stage medium*.
Buffer stage sample solution: Withdraw a 10.0-mL aliquot and pass a portion of the solution under test through a suitable filter of 0.45-µm pore size. Replace the 10.0-mL aliquot withdrawn for analysis with a 10.0-mL aliquot of *Buffer stage medium*.
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 270 nm
Column: 4.6-mm × 25-cm; 5-µm packing L1
Column temperature: 35°
Flow rate: 1 mL/min
Injection volume: 10 µL
Run time: NLT 1.7 times the retention time of lamotrigine
System suitability
Samples: *Acid stage standard solution* and *Buffer stage standard solution*
Suitability requirements
Tailing factor: NMT 2.0
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Acid stage standard solution*, *Acid stage sample solution*, *Buffer stage standard solution*, and *Buffer stage sample solution*
Calculate the percentage (Q_A) of the labeled amount of lamotrigine ($C_9H_7Cl_2N_5$) dissolved in the *Acid stage medium*:

$$\text{Result}_i = (r_U/r_S) \times C_S \times V_A \times (1/L) \times 100$$

r_U = peak response from the *Acid stage sample solution*
r_S = peak response from the *Acid stage standard solution*
C_S = concentration of USP Lamotrigine RS in the *Acid stage standard solution* (mg/mL)
V_A = volume of the *Acid stage medium*, 700 mL
L = label claim (mg/Tablet)

Calculate the concentration (C_i) of lamotrigine ($C_9H_7Cl_2N_5$) in the sample withdrawn from the vessel at each time point (*i*) during the buffer stage:

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

r_U = peak response from the *Buffer stage sample solution* at time point *i*
r_S = peak response from the *Buffer stage standard solution*
C_S = concentration of USP Lamotrigine RS in the *Buffer stage standard solution* (mg/mL)

Calculate the percentage of the labeled amount of lamotrigine ($C_9H_7Cl_2N_5$) dissolved at each time point (*i*) during the buffer stage:

$$\text{Result}_1 = [C_1 \times V_B \times (1/L) \times 100] + (Q_A \times V_S/V_A)$$
$$\text{Result}_2 = \{[(C_2 \times V_B) + (C_1 \times V_S)] \times (1/L) \times 100\} + (Q_A \times V_S/V_A)$$
$$\text{Result}_3 = (\{(C_3 \times V_B) + [(C_2 + C_1) \times V_S]\} \times (1/L) \times 100) + (Q_A \times V_S/V_A)$$

C_i = concentration of lamotrigine in the *Buffer stage sample solution* withdrawn at time point *i* (mg/mL)
V_B = volume of the *Buffer stage medium*, 900 mL
L = label claim (mg/Tablet)
Q_A = the percentage of the labeled amount of lamotrigine dissolved in the *Acid stage medium*
V_S = volume of the sample solution withdrawn at each time point (*i*) during the acid stage or buffer stage (mL)
V_A = volume of the *Acid stage medium*, 700 mL

Tolerances
For Tablets labeled to contain 25, 50, 100, or 200 mg: See *Table 6*.

Table 6

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	2	NMT 10
2	4	NMT 25
3	7	36–61
4	14	NLT 85

The percentages of the labeled amount of lamotrigine ($C_9H_7Cl_2N_5$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.
Test 4: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 4*.
Acid stage medium: 0.01 M hydrochloric acid; 700 mL
Buffer stage stock medium: 7.8 g of sodium phosphate tribasic and 22.5 g of sodium dodecyl sulfate in 1 L of water
Buffer stage medium: *Acid stage medium* and *Buffer stage stock medium* (70:20); 900 mL
Apparatus 2: 50 rpm with sinkers
Times
For Tablets labeled to contain 25, 50, 100, 200, or 300 mg: 2 h in *Acid stage medium*; 9 and 17 h in *Buffer stage medium*
[NOTE—The times in the *Buffer stage medium* include the time in the *Acid stage medium*.]
Procedure: Run the test with *Acid stage medium* for 2 h followed by collecting the *Acid stage medium* sample and replacing it with the same volume of *Acid stage medium*. Add 200 mL of *Buffer stage stock medium* to the above solution. Continue the testing by drawing samples at the time points specified in *Table 7*. Replace each of the volumes withdrawn with an equal volume of the *Buffer stage medium*.
Buffer: Dissolve 4.1 g of potassium phosphate monobasic in 900 mL of water and adjust with dilute phosphoric acid to a pH of 2.0, and then dilute with

water to 1 L. Add 1.25 g of sodium 1-hexanesulfonate to the solution and mix.

Mobile phase: Acetonitrile and *Buffer* (25:75)

Acid stage standard stock solution 1: 0.07 mg/mL of USP Lamotrigine RS prepared as follows. Transfer an appropriate amount of USP Lamotrigine RS to a suitable volumetric flask and add 20% of the flask volume of methanol. Sonicate to dissolve and dilute with *Acid stage medium* to volume. Further dilute this solution with *Acid stage medium* to obtain a final concentration of 0.07 mg/mL.

Acid stage standard stock solution 2: 0.14 mg/mL of USP Lamotrigine RS prepared as follows. Transfer an appropriate amount of USP Lamotrigine RS to a suitable volumetric flask and add 20% of the flask volume of methanol. Sonicate to dissolve and dilute with *Acid stage medium* to volume. Further dilute this solution with *Acid stage medium* to obtain a final concentration of 0.14 mg/mL.

Acid stage standard solution: 0.1 × (*L*/700) mg/mL of USP Lamotrigine RS either from *Acid stage standard stock solution 1* for Tablets labeled to contain 25, 50, 100, and 200 mg, or from *Acid stage standard stock solution 2* for Tablets labeled to contain 300 mg, in *Acid stage medium*, where *L* is the label claim in mg/Tablet. Pass a portion of the solution through a suitable filter of 0.45-µm pore size, discarding the first 2–3 mL of the filtrate.

Buffer stage standard stock solution 1: 0.55 mg/mL of USP Lamotrigine RS prepared as follows. Transfer an appropriate amount of USP Lamotrigine RS to a suitable volumetric flask and add 10% of the flask volume of methanol. Sonicate to dissolve and dilute with *Buffer stage medium* to volume.

Buffer stage standard stock solution 2: 1.1 mg/mL of USP Lamotrigine RS prepared as follows. Transfer an appropriate amount of USP Lamotrigine RS to a suitable volumetric flask and add 20% of the flask volume of methanol. Sonicate to dissolve and dilute with *Buffer stage medium* to volume.

Buffer stage standard solution: (*L*/900) mg/mL of USP Lamotrigine RS either from *Buffer stage standard stock solution 1* for Tablets labeled to contain 25, 50, 100, and 200 mg, or from *Buffer stage standard stock solution 2* for Tablets labeled to contain 300 mg, in *Buffer stage medium*, where *L* is the label claim in mg/Tablet. Pass a portion of the solution through a suitable filter of 0.45-µm pore size, discarding the first 2–3 mL of the filtrate.

Acid stage sample solution: Withdraw a 10.0-mL aliquot and pass a portion of the solution under test through a suitable filter of 0.45-µm pore size, discarding the first 2–3 mL of the filtrate. Replace the 10.0-mL aliquot withdrawn for analysis with a 10.0-mL aliquot of *Acid stage medium*. Pass a portion of the solution through a suitable filter of 0.45-µm pore size, discarding the first 2–3 mL of the filtrate.

Buffer stage sample solution: Withdraw a 10.0-mL aliquot and pass a portion of the solution under test through a suitable filter of 0.45-µm pore size. Replace the 10.0-mL aliquot withdrawn for analysis with a 10.0-mL aliquot of *Buffer stage medium*. Pass a portion of the solution through a suitable filter of 0.45-µm pore size, discarding the first 2–3 mL of the filtrate.

Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 270 nm
Column: 4.6-mm × 25-cm; 5-µm packing L7
Column temperature: 60°
Flow rate: 1 mL/min
Injection volume: 10 µL
Run time: NLT 2 times the retention time of lamotrigine

System suitability
Samples: *Acid stage standard solution* and *Buffer stage standard solution*
Suitability requirements
Tailing factor: NMT 2.0
Relative standard deviation: NMT 2.0%

Analysis
Samples: *Acid stage standard solution*, *Acid stage sample solution*, *Buffer stage standard solution*, and *Buffer stage sample solution*

Calculate the percentage (Q_A) of the labeled amount of lamotrigine ($C_9H_7Cl_2N_5$) dissolved in the *Acid stage medium*:

$$\text{Result}_i = (r_U/r_S) \times C_S \times V_A \times (1/L) \times 100$$

r_U = peak response from the *Acid stage sample solution*
r_S = peak response from the *Acid stage standard solution*
C_S = concentration of USP Lamotrigine RS in the *Acid stage standard solution* (mg/mL)
V_A = volume of the *Acid stage medium*, 700 mL
L = label claim (mg/Tablet)

Calculate the concentration (C_i) of lamotrigine ($C_9H_7Cl_2N_5$) in the sample withdrawn from the vessel at each time point (*i*) during the buffer stage:

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

r_U = peak response from the *Buffer stage sample solution* at time point *i*
r_S = peak response from the *Buffer stage standard solution*
C_S = concentration of USP Lamotrigine RS in the *Buffer stage standard solution* (mg/mL)

Calculate the percentage of the labeled amount of lamotrigine ($C_9H_7Cl_2N_5$) dissolved at each time point (*i*) during the buffer stage:

$$\text{Result}_1 = [C_1 \times V_B \times (1/L) \times 100] + (Q_A \times V_S/V_A)$$
$$\text{Result}_2 = \{[(C_2 \times V_B) + (C_1 \times V_S)] \times (1/L) \times 100\} + (Q_A \times V_S/V_A)$$

C_i = concentration of lamotrigine in the *Buffer stage sample solution* withdrawn at time point *i* (mg/mL)
V_B = volume of the *Buffer stage medium*, 900 mL
L = label claim (mg/Tablet)
Q_A = the percentage of the labeled amount of lamotrigine dissolved in the *Acid stage medium*
V_S = volume of the sample solution withdrawn at each time point (*i*) during the acid stage or buffer stage (mL)
V_A = volume of the *Acid stage medium*, 700 mL

Tolerances
For Tablets labeled to contain 25, 50, 100, 200, or 300 mg: See *Table 7*.

Table 7

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	2	NMT 10
2	9	35–55
3	17	NLT 80

The percentages of the labeled amount of lamotrigine ($C_9H_7Cl_2N_5$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

Test 5: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 5*.

Acid stage medium: 0.01 M hydrochloric acid; 710 mL

Buffer stage stock medium: 3.36 g of anhydrous tribasic sodium phosphate and 22.5 g of sodium dodecyl sulfate in 1 L of water

Buffer stage medium: *Acid stage medium* and *Buffer stage stock medium* (70:20); 900 mL. Adjust with hydrochloric acid or 5 N sodium hydroxide TS, if necessary, to a pH of 6.8.

Apparatus 2: 50 rpm with sinkers

Times

For Tablets labeled to contain 25, 50, 100, or 200 mg: 2 h in *Acid stage medium*; 4, 7, and 17 h in *Buffer stage medium*

[NOTE—The times in the *Buffer stage medium* include the time in *Acid stage medium*.]

Procedure: Run the test with *Acid stage medium* for 2 h followed by collecting the *Acid stage medium* sample. Add 200 mL of *Buffer stage stock medium* to this solution. Continue the testing by drawing samples at the time points specified in *Table 8*.

Buffer: Dissolve 3.45 g of monobasic sodium phosphate in 1 L of water, and adjust with phosphoric acid to a pH of 3.3. To this solution, add 5.77 g of sodium dodecyl sulfate, and mix well.

Mobile phase: Acetonitrile and *Buffer* (45:55)

Standard solution: 0.22 mg/mL of USP Lamotrigine RS in *Mobile phase*. Sonicate to dissolve as needed.

Acid stage sample solution: Withdraw a 10.0-mL aliquot, and pass a portion of the solution under test through a suitable full flow filter of 10-µm pore size.

Buffer stage sample solution: Withdraw a 2.5-mL aliquot, and pass a portion of the solution under test through a suitable full flow filter of 10-µm pore size.

Chromatographic system

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

Mode: LC

Detector: UV 266 nm

Column: 4.6-mm × 5-cm; 3.5-µm packing L1

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: 10 µL

Run time: NLT 1.6 times the retention time of lamotrigine

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution*, *Acid stage sample solution*, and *Buffer stage sample solution*

Calculate the percentage (Q_A) of the labeled amount of lamotrigine ($C_9H_7Cl_2N_5$) dissolved in the *Acid stage medium*:

$$\text{Result}_i = (r_U/r_S) \times C_S \times V_A \times (1/L) \times 100$$

r_U = peak response from the *Acid stage sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Lamotrigine RS in the *Standard solution* (mg/mL)
V_A = volume of the *Acid stage medium*, 710 mL
L = label claim (mg/Tablet)

Calculate the concentration (C_i) of lamotrigine ($C_9H_7Cl_2N_5$) in the sample withdrawn from the vessel at each time point (*i*) during the buffer stage:

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

r_U = peak response from the *Buffer stage sample solution* at time point *i*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Lamotrigine RS in the *Standard solution* (mg/mL)

Calculate the percentage of the labeled amount of lamotrigine ($C_9H_7Cl_2N_5$) dissolved at each time point (*i*) during the buffer stage:

$$\text{Result}_1 = [C_1 \times V_B \times (1/L) \times 100] + (Q_A \times V_S/V_A)$$
$$\text{Result}_2 = \{[C_2 \times (V_B - V_S)] + (C_1 \times V_S)] \times (1/L) \times 100\} + (Q_A \times V_S/V_A)$$
$$\text{Result}_3 = (\{[C_3 \times (V_B - 2V_S)] + [(C_2 + C_1) \times V_S]\} \times (1/L) \times 100) + (Q_A \times V_S/V_A)$$

C_i = concentration of lamotrigine in the *Buffer stage sample solution* withdrawn at time point *i* (mg/mL)
V_B = volume of the *Buffer stage medium*, 900 mL
L = label claim (mg/Tablet)
Q_A = the percentage of the labeled amount of lamotrigine dissolved in the *Acid stage medium*
V_S = volume of the *Sample solution* withdrawn at each time point (*i*), 10 mL for acid stage or 2.5 mL for buffer stage
V_A = volume of the *Acid stage medium*, 710 mL

Tolerances

For Tablets labeled to contain 25, 50, 100, or 200 mg: See *Table 8*.

Table 8

Time Point (*i*)	Time (h)	Amount Dissolved	
		25, 50, and 200 mg/Tablet (%)	100 mg/Tablet (%)
1	2	NMT 10	NMT 10
2	4	10–30	10–30
3	7	35–60	40–65
4	17	NLT 80	NLT 80

The percentages of the labeled amount of lamotrigine ($C_9H_7Cl_2N_5$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

▲**Test 7:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 7*.

Acid stage medium: 0.01 N hydrochloric acid TS; 700 mL, degas by helium sparging before use

Buffer stage stock medium: 7.8 g of sodium phosphate tribasic in 1 L of water, add 2 mL of sodium hydroxide TS and degas by helium sparging, then add 22.5 g of sodium dodecyl sulfate and mix well. Degas by warming the solution to NMT 50° and bring back to 37° before use.

Buffer stage medium: *Acid stage medium* and *Buffer stage stock medium* (70:20), pH 6.8; 900 mL. Adjust with 1 N hydrochloric acid VS or sodium hydroxide TS, if necessary.

Apparatus 1: 75 rpm for Tablets labeled to contain 25, 50, 100, 200, or 300 mg

Apparatus 2: 50 rpm for Tablets labeled to contain 250 mg

Times: 2 h in *Acid stage medium*; see *Table 9* for times in *Buffer stage medium*. The times in the *Buffer stage medium* include the time in *Acid stage medium*.

Procedure: Run the test with *Acid stage medium* for 2 h followed by collecting the *Acid stage medium* sample and replacing it with the same volume of *Acid stage medium*. Add 200 mL of *Buffer stage stock medium* to the above solution. Continue the testing by drawing samples at the time points specified in *Table 9* without replacing the withdrawn volume.

Buffer: 3.85 g/L of ammonium acetate in water, adjust with acetic acid to a pH of 5.60 ± 0.05

Mobile phase: Acetonitrile and *Buffer* (32:68)

Standard stock solution: 2.0 mg/mL of USP Lamotrigine RS prepared as follows. Transfer an appropriate amount of USP Lamotrigine RS to a suitable volumetric flask and add 50% flask volume of methanol. Sonicate with occasional swirling for 5 min or until the Reference Standard is completely dissolved. Dilute with *Buffer stage medium* to volume.

Standard solution: 0.16 mg/mL of USP Lamotrigine RS from *Standard stock solution* in *Buffer stage medium*

Acid stage sample solution: Withdraw a suitable volume of the solution under test and replace the withdrawn aliquot with the same volume of *Acid stage medium*. Pass a portion of the withdrawn solution through a filter of suitable pore size. Discard the first few milliliters of the filtrate.

Buffer stage sample solution: Withdraw a suitable volume of the solution under test and pass a portion of the withdrawn solution through a filter of suitable pore size. Discard the first few milliliters of the filtrate.

Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 306 nm
Column: 4.6-mm × 15-cm; 5-µm packing L7
Column temperature: 30°
Flow rate: 1 mL/min
Injection volume: 10 µL
Run time: NLT 1.4 times the retention time of lamotrigine

System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.0
Relative standard deviation: NMT 2.0%

Analysis
Samples: *Standard solution*, *Acid stage sample solution*, and *Buffer stage sample solution*

Calculate the percentage (Q_A) of the labeled amount of lamotrigine ($C_9H_7Cl_2N_5$) dissolved in the *Acid stage medium*:

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

r_U = peak response from the *Acid stage sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Lamotrigine RS in the *Standard solution* (mg/mL)
V_A = volume of the *Acid stage medium*, 700 mL
L = label claim (mg/Tablet)

Calculate the concentration (C_i) of lamotrigine ($C_9H_7Cl_2N_5$) in the sample withdrawn from the vessel at each time point (i) during the buffer stage:

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

r_U = peak response from the *Buffer stage sample solution* at time point i
r_S = peak response from the *Standard solution*
C_S = concentration of USP Lamotrigine RS in the *Standard solution* (mg/mL)

Calculate the percentage of the labeled amount of lamotrigine ($C_9H_7Cl_2N_5$) dissolved at each time point (i) during the buffer stage:

$$\text{Result}_2 = [C_2 \times V_B \times (1/L) \times 100] + (Q_A \times V_S/V_A)$$
$$\text{Result}_3 = \{[C_3 \times (V_B - V_S) + (C_2 \times V_S)] \times (1/L) \times 100\} + (Q_A \times V_S/V_A)$$
$$\text{Result}_4 = (\{[C_4 \times (V_B - 2V_S)] + [(C_3 + C_2) \times V_S]\} \times (1/L) \times 100) + (Q_A \times V_S/V_A)$$

C_i = concentration of lamotrigine in the *Buffer stage sample solution* withdrawn at time point i (mg/mL)
V_B = volume of the *Buffer stage medium*, 900 mL
L = label claim (mg/Tablet)
Q_A = percentage of the labeled amount of lamotrigine dissolved in the *Acid stage medium*
V_S = volume of the *Sample solution* withdrawn at each time point (i)
V_A = volume of the *Acid stage medium*, 700 mL

Tolerances: See *Table 9*.

Table 9

Time Point (*i*)	Time (h)	Amount Dissolved					
		25 mg/Tablet (%)	50 mg/Tablet (%)	100 mg/Tablet (%)	200 mg/Tablet (%)	250 mg/Tablet (%)	300 mg/Tablet (%)
1	2	NMT 10	NMT 10	NMT 10	NMT 10	NMT 10	NMT 10
2	4	10–30	10–30	10–30	10–30	8–25	10–28
	7	—	—	53–73	—	—	—
	8	50–70	—	—	50–70	—	50–70
3	9	—	45–65	—	—	55–75	—

Table 9 *(continued)*

Time Point (*i*)	Time (h)	Amount Dissolved					
		25 mg/ Tablet (%)	50 mg/ Tablet (%)	100 mg/ Tablet (%)	200 mg/ Tablet (%)	250 mg/ Tablet (%)	300 mg/ Tablet (%)
	10	—	—	NLT 80	—	—	—
	11	—	—	—	—	—	NLT 80
	12	NLT 80	—	—	NLT 80	—	—
	14	—	NLT 80	—	—	—	—
4	15	—	—	—	—	NLT 85	—

The percentages of the labeled amount of lamotrigine ($C_9H_7Cl_2N_5$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.▲ (RB 1-Feb-2019)

- **UNIFORMITY OF DOSAGE UNITS** ⟨905⟩**:** Meet the requirements

IMPURITIES

Change to read:

- **ORGANIC IMPURITIES**

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

Diluent 1: Acetonitrile, methanol, and 0.1 M hydrochloric acid (10:20:70)

Diluent 2: Acetonitrile, methanol, and water (10:20:70)

System suitability stock solution: 0.025 mg/mL of USP Lamotrigine Related Compound C RS in *Diluent 1*

System suitability solution: 1.25 µg/mL of USP Lamotrigine Related Compound C RS and 0.25 mg/mL of USP Lamotrigine RS in *Diluent 2* prepared as follows. Transfer a suitable amount of USP Lamotrigine RS to a suitable volumetric flask. Transfer a suitable volume of *System suitability stock solution* to the flask. Dissolve and dilute with *Diluent 2* to volume.

System suitability

Sample: *System suitability solution*

Suitability requirements

Resolution: NLT 10 between the lamotrigine and lamotrigine related compound C peaks

Signal-to-noise ratio: NLT 100 for lamotrigine related compound C

Analysis

Sample: *Sample solution*

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

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

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

r_T = sum of all of the impurity peak responses and the lamotrigine peak response from the *Sample solution*

Acceptance criteria: See ▲*Table 10*.▲ (RB 1-Feb-2019) Disregard peaks less than 0.05%.

▲Table 10▲ (RB 1-Feb-2019)

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Lamotrigine	1.0	—
Lamotrigine relatedcompound C	1.7	0.3
Lamotrigine dimer[a]	6.0	0.2
Any individual unspecified degradation product	—	0.2
Total impurities	—	0.5

[a] This is either lamotrigine *o*-dimer [N^5,$N^{5'}$-methylenebis(6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine)] or lamotrigine *p*-dimer [N^3,$N^{3'}$-methylenebis(6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine)].

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers. 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.
- **USP REFERENCE STANDARDS** ⟨11⟩

USP Lamotrigine RS

USP Lamotrigine Related Compound C RS

3-Amino-6-(2,3-dichlorophenyl)-1,2,4-triazin-5(4*H*)-one.

$C_9H_6Cl_2N_4O$ 257.08