

Lamotrigine Extended-Release Tablets

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Posting Date	25-Jan-2019
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Expert Committee	Chemical Medicines Monographs 4

In accordance with section 7.04 (c) of the 2015–2020 Rules and Procedures of the Council of Experts and the [Pending Monograph Guideline](#), this is to provide notice that the Chemical Medicines Monographs 4 Expert Committee intends to revise the Lamotrigine Extended-Release Tablets monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to add *Dissolution Test 8* to the monograph.

- *Dissolution Test 8* was validated using a Waters Corporation Symmetry Shield RP8 brand of L7 column. The typical retention time for lamotrigine is about 6.7 min.

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

The proposed revision is contingent on FDA approval of a product that meets the proposed monograph specifications. The proposed revision will be published as a Revision Bulletin and an official date will be assigned to coincide as closely as possible with the FDA approval of the associated product.

See below for additional information about the proposed text.¹

Should you have any questions, please contact Ren-Hwa Yeh, Senior Scientific Liaison to the Chemical Medicines Monographs 4 Expert Committee (301-998-6818 or rhy@usp.org).

¹ This text is not the official version of a *USP–NF* monograph and may not reflect the full and accurate contents of the currently official monograph. Please refer to the current edition of the *USP–NF* for official text.

USP provides this text to indicate changes that we anticipate will be made official once the product subject to this proposed revision under the Pending Monograph Program receives FDA approval. Once FDA approval is granted for the associated revision request, a Revision Bulletin will be posted that will include the changes indicated herein, as well as any changes indicated in the product's final approval, combined with the text of the monograph as effective on the date of approval. Any revisions made to a monograph under the Pending Monograph Program that are posted without prior publication for comment in the *Pharmacopeial Forum* must also meet the requirements outlined in the [USP Guideline on Use of Accelerated Processes for Revisions to the USP–NF](#).

Lamotrigine Extended-Release Tablets

DEFINITION

Lamotrigine Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of lamotrigine (C₉H₇Cl₂N₃).

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 (C₉H₇Cl₂N₃) 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 (C₉H₇Cl₂N₃) 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%

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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 ($C_9H_7Cl_2N_3$) 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*.

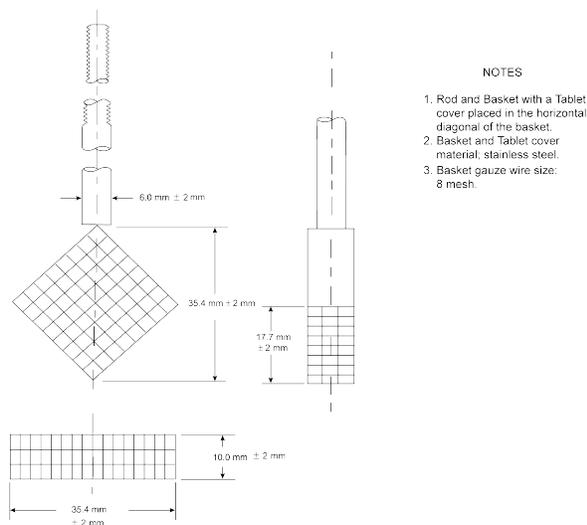


Figure 1. Stationary tablet basket.

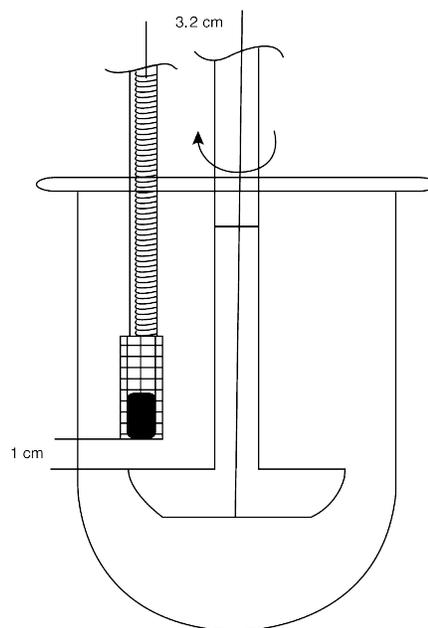


Figure 2. Drug release stationary tablet basket configuration diagram.

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- μ m 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- μ m 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 \times 15-cm; 5- μ m packing L7

Flow rate: 1 mL/min

Injection volume

For 25-mg Tablets: 80 μ L

For 50-mg Tablets: 40 μ L

For 100-mg Tablets: 20 μ L

For 200- or 300-mg Tablets: 10 μ L

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*.

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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- μ m 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- μ m 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 \times 25-cm; 5- μ m packing L1

Column temperature: 35°

Flow rate: 1 mL/min

Injection volume: 10 μ L

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:

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

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: $0.1 \times (L/700)$ 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- μ m 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- μ m 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- μ m 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- μ m 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- μ m 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- μ m 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 \times 25-cm; 5- μ m packing L7

Column temperature: 60°

Flow rate: 1 mL/min

Injection volume: 10 μ L

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:

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

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

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*.

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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- μ m 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- μ m pore size.

Chromatographic system

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

Mode: LC

Detector: UV 266 nm

Column: 4.6-mm \times 5-cm; 3.5- μ m packing L1

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: 10 μ L

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:

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

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:

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

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
3	7	—	—	53–73	—	—	—
	8	50–70	—	—	50–70	—	50–70
	9	—	45–65	—	—	55–75	—
4	10	—	—	NLT 80	—	—	—
	11	—	—	—	—	—	NLT 80
	12	NLT 80	—	—	NLT 80	—	—
	14	—	NLT 80	—	—	—	—
	15	—	—	—	—	NLT 85	—

8 Lamotrigine

Notice of Intent to Revise
Official: To Be Determined

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)

▲ **Test 8:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 8*.

Acid stage medium, Buffer stage stock medium, and Buffer stage medium: Prepare as directed in *Dissolution Test 3*.

Apparatus 2: 50 rpm

Times: 2 h in *Acid stage medium*; 6, 11, 17, and 24 h in *Buffer stage medium*. 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. 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 10*.

Buffer: 1.6 g/L each of anhydrous sodium acetate and trichloroacetic acid in water and adjust with either glacial acetic acid or sodium hydroxide TS to a pH of 4.7

Mobile phase: Acetonitrile and *Buffer* (30:70)

Standard stock solution: 1.1 mg/mL of USP Lamotrigine RS in methanol. Sonicate to dissolve as needed.

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. Pass the solution through a suitable filter of 0.45- μ m pore size. Discard the first few milliliters of the filtrate.

Acid stage sample solution: Withdraw a 1.0-mL aliquot and pass a portion of the solution under test through a suitable filter of 0.45- μ m pore size.

Buffer stage sample solution: Withdraw a 1.0-mL aliquot and pass a portion of the solution under test through a suitable filter of 0.45- μ m pore size.

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm \times 25-cm; 5- μ m packing L7

Flow rate: 1.2 mL/min

Injection volume

For Tablets labeled to contain 25, 50, 100, or 200 mg: 10 μ L

For Tablets labeled to contain 250 or 300 mg: 5 μ L

Run time: NLT 1.5 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:

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

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

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

$$\text{Result}_5 = \{[(C_5 \times V_B) + [(C_4 + C_3 + C_2) \times V_S]] \times (1/L) \times 100\} + (Q_A \times V_S/V_A)$$

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) during the acid stage or buffer stage (mL)

V_A = volume of the *Acid stage medium*, 700 mL

Tolerances: See *Table 10*.

Table 10

Time Point (i)	Time (h)	Amount Dissolved (%)
1	2	NMT 10
2	6	14–34
3	11	42–70
4	17	NLT 70
5	24	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*. ▲ (TBD)

• **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 11.▲ (TBD) Disregard peaks less than 0.05%.

Table ▲11▲ (TBD)

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Lamotrigine	1.0	—
Lamotrigine related compound 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.
C₉H₆Cl₂N₄O 257.08