Mirtazapine Tablets

Type of Posting	Notice of Intent to Revise
Posting Date	16-Dec-2022
Targeted Official Date	To Be Determined, Revision Bulletin
Expert Committee	Small Molecules 4

In accordance with the Rules and Procedures of the Council of Experts and the Pending Monograph Guideline, this is to provide notice that the Small Molecules 4 Expert Committee intends to revise the Mirtazapine Tablets monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to revise the Mirtazapine Tablets monograph to add *Dissolution Test 2*. *Labeling* information has been incorporated to support the inclusion of *Dissolution Test 2*.

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 Yanyin Yang, Senior Scientist II (301-692-3623 or yanyin.yang@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*.

Notice of Intent to Revise
Official: To Be Determined

Mirtazapine Tablets

DEFINITION
Mirtazapine Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of mirtazapine ($C_{17}H_{19}N_3$).

IDENTIFICATION
- **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197K

  Extraction mixture: *n*-hexane and water (1:1)

  Sample: Transfer an amount equivalent to 30 mg of mirtazapine from finely powdered Tablets to a suitable centrifuge tube. Add *Extraction mixture* to obtain a solution of 1 mg/mL of mirtazapine in *n*-hexane. Shake for 5 min, and centrifuge. Decant, and evaporate the supernatant.

  Standard: Dissolve USP Mirtazapine RS in *Extraction mixture* to obtain a solution having a concentration of about 1 mg/mL of mirtazapine in *n*-hexane. Shake for 5 min, and centrifuge. Decant, and evaporate the supernatant.
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY
- **Procedure**

  Diluent: Acetonitrile and water (1:1)

  Buffer: Dissolve 18.0 g of tetramethylammonium hydroxide pentahydrate in 950 mL of water. Adjust with phosphoric acid to a pH of 7.4, and dilute with water to 1 L.

  Mobile phase: Acetonitrile, methanol, tetrahydrofuran, and *Buffer* (15: 12.5: 7.5: 65)

  Standard solution: 0.3 mg/mL of USP Mirtazapine RS in *Diluent*

  Sample solution: Nominally 0.3 mg/mL of mirtazapine (from an amount equivalent to the weight of 1 Tablet from NLT 20 finely powdered Tablets) in *Diluent*. Shake vigorously for 10 min, centrifuge an aliquot, and use the clear supernatant.

  Chromatographic system

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

  Mode: LC

  Detector: UV 290 nm

  Column: 4.6-mm × 25-cm; packing L1

  Column temperature: 40°

  Flow rate: 1.5 mL/min

  Injection volume: 10 µL

  System suitability

  Sample: *Standard solution*

  Suitability requirements

  Column efficiency: NLT 7000 theoretical plates

  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 mirtazapine ($C_{17}H_{19}N_3$) 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 Mirtazapine RS in the *Standard solution* (mg/mL)

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

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

- **Dissolution** ⟨711⟩

▲**Test 1**▲ (TBD)

Medium: 0.1 N hydrochloric acid; 900 mL

Apparatus 2: 50 rpm

Time: 15 min

Sample solution: Pass a portion of the solution under test through a suitable filter. Dilute with *Medium*, if necessary.

Standard solution: USP Mirtazapine RS in *Medium* in a concentration similar to the one expected in the *Sample solution*

Instrumental conditions

(See *Ultraviolet-Visible Spectroscopy* ⟨857⟩.)

Mode: UV

Analytical wavelength: 315 nm

Analysis

Samples: *Sample solution* and *Standard solution*

Calculate the percentage of the labeled amount of mirtazapine ($C_{17}H_{19}N_3$) dissolved:

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

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

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

V = volume of the *Medium*, 900 mL

L = label claim (mg/Tablet)

Tolerances: NLT 80% (Q) of the labeled amount of mirtazapine ($C_{17}H_{19}N_3$) is dissolved.

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

Protect all solutions containing mirtazapine from light.

Medium: 0.1 N hydrochloric acid; 500 mL

Apparatus 2: 50 rpm

Time: 15 min

Buffer: Dissolve 1.36 g of monobasic potassium phosphate in 1000 mL of water and add 1.0 mL of ammonium hydroxide. Adjust with phosphoric acid or potassium hydroxide to a pH of 2.0.

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

Standard solution: 0.09 mg/mL of USP Mirtazapine RS in *Medium*

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size.

Chromatographic system

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

Mode: LC

Detector: UV 290 nm

Column: 4.6-mm × 15-cm; 3.5-µm packing L7

Column temperature: 35°

Flow rate: 1 mL/min

Injection volume: 10 µL

Run time: NLT 1.5 times the retention time of mirtazapine

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 percentage of the labeled amount of mirtazapine ($C_{17}H_{19}N_3$) dissolved:

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

r_U = peak response of mirtazapine from the *Sample solution*

r_S = peak response of mirtazapine from the *Standard solution*

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

V = volume of *Medium*, 500 mL

L = label claim (mg/Tablet)

Tolerances: NLT 80% (*Q*) of the labeled amount of mirtazapine ($C_{17}H_{19}N_3$) is dissolved. ▲ (TBD)

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

IMPURITIES

- **Organic Impurities**

Diluent, Buffer, and **Mobile phase:** Proceed as directed in the *Assay*.

System suitability solution: 1.5 mg/mL of USP Mirtazapine Resolution Mixture RS in *Diluent*

Standard solution: 0.015 mg/mL of USP Mirtazapine RS in *Diluent*

Sample solution: 1.5 mg/mL of mirtazapine (from an amount equivalent to the weight of 1 Tablet from NLT 20 finely powdered Tablets) in *Diluent*. Shake vigorously for 10 min, centrifuge an aliquot, and use the clear supernatant.

Chromatographic system

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

Mode: LC

Detector: UV 240 nm

Column: 4.6-mm × 25-cm; packing L1

Column temperature: 40°

Flow rate: 1.5 mL/min

Injection volume: 10 µL

Run time: 2 times the retention time of mirtazapine

System suitability

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

[NOTE—The relative retention times are listed in *Table 1*.]

Suitability requirements

Resolution: NLT 1.5 between acyclomirtazapine methyl derivative (impurity E) and 10-ketomirtazpine (impurity F), *System suitability solution*

Tailing factor: NMT 2.0, *Standard solution*

Relative standard deviation: NMT 10.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Tablets taken:

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

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

r_S = mirtazapine peak response from the *Standard solution*

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

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

F = relative response factor for the corresponding impurity (see *Table 1*)

Acceptance criteria: See *Table 1*.

Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Mirtazapine *N*-oxide[a]	0.2	0.8	0.2
Acyclomirtazapine alcohol[b,g]	0.3	—	—
1-Ketomirtazpine[c]	0.35	1.0	0.2
Desmethylmirtazapine[d,g]	0.4	—	—
Mirtazapine	1.0	—	—
Acyclomirtazapine methyl derivative[e,g]	1.3	—	—
10-Ketomirtazapine[f]	1.35	5.0	0.2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Any individual unspecified degradation product	—	1.0	0.2
Total impurities	—	—	2.0

[NOTE—Disregard any peak representing less than 0.05% of the main peak and any peak that is due to the *Diluent*.]

[a] 1,2,3,4,10,14b-Hexahydro-2-methylpyrazino[2,1-*a*]pyrido[2,3-*c*][2]benzazepine 2-oxide. (Impurity A)

[b] (2-(4-Methyl-2-phenylpiperazin-1-yl)pyridin-3-yl)methanol. (Impurity B)

[c] (2-Methyl-3,4,10,14b-tetrahydrobenzo[*c*]pyrazino[1,2-*a*]pyrido[3,2-*f*]azepin-1(2*H*)-one. (Impurity C)

[d] 1,2,3,4,10,14b-Hexahydropyrazino[2,1-*a*]pyrido[2,3-*c*][2]benzazepine. (Impurity D)

[e] 4-Methyl-1-(3-methylpyridin-2-yl)-2-phenylpiperazine. (Impurity E)

[f] 2-Methyl-1,2,3,4-tetrahydrobenzo[*c*]pyrazino[1,2-*a*]pyrido[3,2-*f*]azepin-10(14b*H*)-one. (Impurity F)

[g] Process impurity. Included for identification purposes only. Not to be included in *Total impurities*.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers, and store at controlled room temperature.

Add the following:

▲● **LABELING:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.▲ (TBD)

- **USP REFERENCE STANDARDS** ⟨11⟩

USP Mirtazapine RS

USP Mirtazapine Resolution Mixture RS

Mirtazapine.

Impurity A: 1,2,3,4,10,14b-Hexahydro-2-methylpyrazino[2,1-*a*]pyrido[2,3-*c*][2]benzazepine 2-oxide.

Impurity B: (2-(4-Methyl-2-phenylpiperazin-1-yl)pyridin-3-yl)methanol.

Impurity C: (2-Methyl-3,4,10,14b-tetrahydrobenzo[*c*]pyrazino[1,2-*a*]pyrido[3,2-*f*]azepin-1(2*H*)-one.

Impurity D: [NOTE—This impurity may be available either as the free base form or as the hydrochloride salt form.] 1,2,3,4,10,14b-Hexahydropyrazino[2,1-*a*]pyrido[2,3-*c*][2]benzazepine or 1,2,3,4,10,14b-Hexahydropyrazino[2,1-*a*]pyrido[2,3-*c*][2]benzazepine hydrochloride.

Impurity E: 4-Methyl-1-(3-methylpyridin-2-yl)-2-phenylpiperazine.

Impurity F: 2-Methyl-1,2,3,4-tetrahydrobenzo[*c*]pyrazino[1,2-*a*]pyrido[3,2-*f*]azepin-10(14b*H*)-one.

Page Information:

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