Dronedarone Tablets

Type of Posting	Notice of Intent to Revise
Posting Date	29–May–2020
Targeted Official Date	To Be Determined, Revision Bulletin
Expert Committee	Chemical Medicines Monographs 2

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 2 Expert Committee intends to revise the Dronedarone Tablets monograph.

Based on the supporting data received from a manufacturer awaiting FDA final approval, the Expert Committee proposes to add *Dissolution Test 3* to the monograph. The Notice of Intent to Revise regarding *Dissolution Test 2* was previously posted. *Labeling* information also has been incorporated to support the inclusion of *Dissolution Test 3*.

The proposed revision is contingent on FDA final 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 Edith Chang, Senior Scientific Liaison–Team Leader (301-816-8392 or yec@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*.

Dronedarone Tablets

DEFINITION

Dronedarone Tablets contain an amount of dronedarone hydrochloride equivalent to NLT 95.0% and NMT 105.0% of the labeled amount of dronedarone free base ($C_{31}H_{44}N_2O_5S$).

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*.

● **B.** The UV absorption spectra of the dronedarone peak in the *Sample solution* exhibit maxima and minima at the same wavelengths as those of the corresponding peak of the *Standard solution*, as obtained in the *Assay*.

ASSAY

● **Procedure**

Buffer: Combine 2.0 mL of triethylamine with 1 L of water and adjust with phosphoric acid to a pH of 3.0.

Mobile phase: Acetonitrile and *Buffer* (50:50)

System suitability stock solution: 0.2 mg/mL each of USP Dronedarone Hydrochloride RS and USP Dronedarone Related Compound A RS in methanol

System suitability solution: 0.01 mg/mL each of USP Dronedarone Hydrochloride RS and USP Dronedarone Related Compound A RS in *Mobile phase* from the *System suitability stock solution*

Standard stock solution: 2.13 mg/mL of USP Dronedarone Hydrochloride RS in methanol

Standard solution: 0.11 mg/mL of USP Dronedarone Hydrochloride RS in *Mobile phase* from the *Standard stock solution*

Sample stock solution: Nominally equivalent to 4 mg/mL of dronedarone in methanol prepared as follows. Dissolve and dilute in methanol to volume, an amount equivalent to 400 mg of dronedarone from NLT 20 finely powdered Tablets, taken in a 100-mL volumetric flask. Sonicate for about 5 min and allow to settle at room temperature.

Sample solution: Nominally equivalent to 0.1 mg/mL of dronedarone in *Mobile phase* from the *Sample stock solution*. Pass through a suitable filter of 0.45-µm pore size and discard the first 3 mL of the filtrate.

Chromatographic system

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

Mode: LC

Detectors

Assay: UV 288 nm

Identification test B: UV diode array

Column: 4.6-mm × 25-cm; 5-µm packing L10

Flow rate: 0.8 mL/min

Injection volume: 20 µL

Run time: NLT 2.15 times the retention time of dronedarone

System suitability

Sample: *System suitability solution*

[Note—The relative retention times for dronedarone related compound A and dronedarone are 0.7 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 8 between dronedarone and dronedarone related compound A

Tailing factor: 0.8–2.1 for dronedarone

Relative standard deviation: NMT 1.5%, for dronedarone

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of dronedarone free base ($C_{31}H_{44}N_2O_5S$) in the portion of Tablets taken:

$$(r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

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

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

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

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

M_{r1} = molecular weight of dronedarone free base, 556.76

M_{r2} = molecular weight of dronedarone hydrochloride, 593.22

Acceptance criteria: 95.0%–105.0%

PERFORMANCE TESTS

Change to read:

- **Dissolution** ⟨711⟩

▲Test 1▲ (TBD)

Medium: 13.61 g/L of monobasic potassium phosphate in water. Adjust with 0.1 M hydrochloric acid or 0.1 M sodium hydroxide as needed to a pH of 4.5; 1000 mL

Apparatus 2: 75 rpm, with sinker ring

Times: 30 and 90 min

Standard solution: 0.43 mg/mL of USP Dronedarone Hydrochloride RS prepared as follows. Dissolve a suitable amount of USP Dronedarone Hydrochloride RS in 2% of the total volume of methanol and dilute with *Medium* to volume.

Sample solution: Pass a portion of sample under test through a suitable filter.

Instrumental conditions

Analytical wavelength: UV 288 nm

Cell: 1 mm

Blank: *Medium*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of dronedarone dissolved:

$$\text{Result} = (A_U/A_S) \times C_S \times V \times (1/L) \times (M_{r1}/M_{r2}) \times 100$$

A_U = absorbance from the *Sample solution*

A_S = absorbance from the *Standard solution*

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

V = volume of *Medium*, 1000 mL

L = label claim (mg/Tablet)

M_{r1} = molecular weight of dronedarone free base, 556.76

M_{r2} = molecular weight of dronedarone hydrochloride, 593.22

Tolerances

30 min: 20.0%–60.0% of the labeled amount of dronedarone free base ($C_{31}H_{44}N_2O_5S$) is dissolved.

90 min: NLT 80% (*Q*) of the labeled amount of dronedarone free base ($C_{31}H_{44}N_2O_5S$) is dissolved.

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

Medium: 6.8 g/L of potassium phosphate, monobasic in water. Adjust with diluted phosphoric acid [about 7% (v/v)] or diluted sodium hydroxide (about 2 N) to a pH of 4.5; 1000 mL.

Apparatus 2: 75 rpm

Times: 30 and 90 min

Buffer: 6.8 g/L of potassium phosphate, monobasic in water. Adjust with phosphoric acid to a pH of 2.5.

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

Standard solution: 0.425 mg/mL of USP Dronedarone Hydrochloride RS prepared as follows. Dissolve a suitable amount of USP Dronedarone Hydrochloride RS in 10% of the total volume of methanol. Sonicate to dissolve and dilute with *Medium* to volume.

Sample solution: At the times specified, withdraw 10 mL of the solution under test. Replace the aliquot withdrawn for analysis with an equal volume of fresh portions of *Medium* maintained at 37°. Pass the solution through a suitable filter.

Chromatographic system

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

Mode: LC

Detector: UV 288 nm

Column: 4.6-mm × 15-cm; 5-µm packing L1

Column temperature: 40°

Flow rate: 1 mL/min

Injection volume: 5 µL

Run time: NLT 2.5 times the retention time of dronedarone

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 of dronedarone ($C_{31}H_{44}N_2O_5S$) in the sample withdrawn from the vessel at each time point (*i*):

$$\text{Result} = (r_U/r_S) \times C_S \times (M_{r1}/M_{r2})$$

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

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

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

M_{r1} = molecular weight of dronedarone free base, 556.76

M_{r2} = molecular weight of dronedarone hydrochloride, 593.22

Calculate the percentage of the labeled amount of dronedarone ($C_{31}H_{44}N_2O_5S$) dissolved at each time point (i):

$$Result_1 = (C_1 \times V \times (1/L) \times 100$$

$$Result_2 = [(C_2 \times V) + (C_1 \times V_S)] \times (1/L) \times 100$$

C_i = concentration of dronedarone in the portion of sample withdrawn at the specified time point (mg/mL)

V = volume of *Medium*, 1000 mL

L = label claim (mg/Tablet)

V_S = volume of the *Sample solution*withdrawn at each time point (mL)

Tolerances: See *Table 1*.

Table 1

Time Point (*i*)	Time (min)	Amount Dissolved (%)
1	30	NLT 35
2	90	NLT 80 (*Q*)▲ (TBD)

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

IMPURITIES

- **Organic Impurities**

Buffer, Mobile phase, and **System suitability stock solution:** Proceed as directed in the *Assay*.

System suitability solution: 0.01 mg/mL each of USP Dronedarone Hydrochloride RS and USP Dronedarone Related Compound A RS prepared as follows. To a suitable amount of *System suitability stock solution*, add 20% of the total volume of methanol and dilute with *Mobile phase* to volume.

Standard stock solution: 0.4 mg/mL of USP Dronedarone Hydrochloride RS in methanol

Standard solution: 0.002 mg/mL of USP Dronedarone Hydrochloride RS prepared as follows. To a suitable amount of *Standard stock solution*, add 25% of the total volume of methanol and dilute with *Mobile phase* to volume.

Sensitivity solution: 0.0005 mg/mL of USP Dronedarone Hydrochloride RS prepared as follows. To a suitable amount of the *Standard solution*, add 20% of the total volume of methanol and dilute with *Mobile phase* to volume.

Sample stock solution: Nominally equivalent to 4 mg/mL of dronedarone in methanol prepared as follows. Dissolve and dilute in methanol to volume, an amount equivalent to 400 mg of dronedarone from NLT 20 finely powdered Tablets, taken in a 100-mL volumetric flask. Sonicate for about 5 min and allow to settle at room temperature.

Sample solution: Nominally equivalent to 1 mg/mL of dronedarone in *Mobile phase* from *Sample stock solution*. Pass through a suitable filter of 0.45-µm pore size and discard the first 3 mL of the filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 246 nm

Column: 4.6-mm × 25-cm; 5-µm packing L10

Flow rate: 0.8 mL/min

Injection volume: 20 µL

Run time: NLT 3.6 times the retention time of dronedarone

System suitability

Samples: *System suitability solution* and *Sensitivity solution*

[NOTE—The relative retention times for dronedarone related compound A and dronedarone are 0.7 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 8 between dronedarone and dronedarone related compound A, *System suitability solution*

Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Analysis

Samples: *Standard solution* and *Sample solution*

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

$$(r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

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

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

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

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

M_{r1} = molecular weight of dronedarone free base, 556.76

M_{r2} = molecular weight of dronedarone hydrochloride, 593.22

Acceptance criteria: Disregard peaks less than 0.05%.

Any unspecified impurity: NMT 0.20%

Total impurities: NMT 0.4%

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** 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 Dronedarone Hydrochloride RS

USP Dronedarone Related Compound A RS

N-(2-Butyl-3-{4-[3-(butylamino)propoxy]benzoyl}benzofuran-5-yl)methanesulfonamide.

$C_{27}H_{36}N_2O_5S$ 500.65

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