Dronedarone Tablets

Type of Posting	Notice of Intent to Revise
Posting Date	28–Dec–2018
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 approval, the Expert Committee proposes to add *Dissolution Test 2* to the monograph to accommodate FDA-approved drug products with different tolerances than the existing dissolution test. *Labeling* information also 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 Edith Chang, Senior Scientific Liaison to the Chemical Medicines Monographs 2 Expert Committee (301-816-8392 or vec@usp.org).

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

Medium: 13.61 g/L of monobasic potassium phosphate in water. Adjust with 0.1 N hydrochloric acid or 0.1 N sodium hydroxide as needed to a pH of 4.5; 1000 mL.
Apparatus 2: 75 rpm, with a sinker
Times: 45 and 90 min
Standard stock solution: 0.42 mg/mL of USP Dronedarone Hydrochloride RS prepared as follows. Dissolve a suitable amount of USP Dronedarone Hydrochloride RS in 5% of the total volume of methanol. Sonicate to dissolve and dilute with *Medium* to volume.
Standard solution: 0.0252 mg/mL of USP Dronedarone Hydrochloride RS in *Medium* from the *Standard stock solution*. Pass through a suitable filter.
Sample solution: At the times specified, withdraw 10 mL of the solution under test. Replace the aliquot withdrawn for analysis with equal volume of fresh portions of *Medium* maintained at 37°. Pass solution through a suitable filter. Transfer 3 mL of filtrate to a 50-mL volumetric flask and dilute with *Medium* to volume.
Instrumental conditions
Mode: UV
Analytical wavelength: 288 nm
Cell: 1 mm
Blank: *Medium*
System suitability
Sample: *Standard solution*
Suitability requirements
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*:

$$\text{Result} = (A_U/A_S) \times C_S \times D \times (M_{r1}/M_{r2})$$

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)
D = dilution factor of the *Sample solution*, 16.7
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*:

$$\text{Result}_1 = C_I \times V \times (1/L) \times 100$$
$$\text{Result}_2 = [(C_2 \times V) + (C_I \times V_S)] \times (1/L) \times 100$$

C_i = concentration of dronedarone in the *Sample solution* 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 withdrawn at each time point *i* (mL)

Tolerances: See *Table 1*.

Table 1

Time Point (*i*)	Time (min)	Amount Dissolved
1	45	NLT 50%
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