Itraconazole Capsules

Type of Posting	Revision Bulletin
Posting Date	31–May–2019
Official Date	01–August–2019
Expert Committee	Chemical Medicines Monographs 1
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Chemical Medicines 1 Expert Committee has revised the Itraconazole Capsules monograph. The purpose for the revision is to add *Dissolution Test 2* to accommodate FDA-approved drug products with different tolerances than the existing dissolution test. *Labeling* has been incorporated to support the inclusion of *Dissolution Test 2*.

Additionally, in the test for *Organic Impurities*, the relative response factors in *Table 2* have been deleted as they pertain to process impurities, and footnote b is updated to clarify that the process impurities are not monitored or included in the calculation for total impurities.

The Itraconazole Capsules Revision Bulletin supersedes the version that is scheduled to become official in the *First Supplement to USP 42–NF 37*.

Should you have any questions, please contact Shankari Shivaprasad, Senior Scientific Liaison-Team Leader (301-230-7426 or sns@usp.org).

Add the following:

▲Itraconazole Capsules

DEFINITION
Itraconazole Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of itraconazole ($C_{35}H_{38}Cl_2N_8O_4$).

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 spectrum of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY
- **PROCEDURE**

Solution A: 5.8 g/L of monobasic ammonium phosphate in water. Adjust with phosphoric acid to a pH of 2.0. Pass through a suitable filter of 0.45-µm pore size.
Solution B: Acetonitrile and tetrahydrofuran (90:10)
Mobile phase: *Solution A* and *Solution B* (45:55)
Diluent: Methanol and tetrahydrofuran (50:50)
Standard solution: 0.1 mg/mL of USP Itraconazole RS in *Diluent*. Sonicate, if necessary, to dissolve.
Sample stock solution: Nominally 1 mg/mL of itraconazole in *Diluent* prepared as follows. Transfer an amount nominally equivalent to 100 mg of itraconazole, from the contents of NLT 20 Capsules, to a 100-mL volumetric flask. Add 70 mL of *Diluent*, and sonicate for about 30 min. Dilute with *Diluent* to volume. Pass through a suitable filter of 0.45-µm pore size.
Sample solution: Nominally 0.1 mg/mL of itraconazole in *Diluent* from *Sample stock solution*
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 225 nm. For *Identification B*, use a diode array detector in the range of 200–400 nm.
Column: 4.6-mm × 15-cm; 3-µm packing L1
Column temperature: 30°
Flow rate: 1.5 mL/min
Injection volume: 10 µL
Run time: NLT 2 times the retention time of itraconazole
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 itraconazole ($C_{35}H_{38}Cl_2N_8O_4$) in the portion of Capsules taken:

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

r_U = peak response of itraconazole from the *Sample solution*
r_S = peak response of itraconazole from the *Standard solution*
C_S = concentration of USP Itraconazole RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of itraconazole in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

- **DISSOLUTION** ⟨711⟩

▲Test 1▲ (RB 1-Aug-2019)
Medium: 0.25% (w/v) sodium lauryl sulfate in 0.1 N hydrochloric acid; 900 mL
Apparatus 2: 75 rpm; with a three-prong sinker
Time: 45 min
Standard stock solution: 0.55 mg/mL of USP Itraconazole RS in 40% glacial acetic acid. Sonicate, if necessary, to dissolve.
Standard solution: 0.02 mg/mL of USP Itraconazole RS in *Medium* from *Standard stock solution*
Sample solution: A filtered portion of the solution under test, suitably diluted with *Medium*, to obtain a concentration similar to that of the *Standard solution*.
Blank: *Medium*
Instrumental conditions
Mode: UV
Analytical wavelength: 260 nm
System suitability
Sample: *Standard solution*
Suitability requirements
Relative standard deviation: NMT 2.0% for 5 replicate injections
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of itraconazole ($C_{35}H_{38}Cl_2N_8O_4$) released:

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

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of USP Itraconazole RS in the *Standard solution* (mg/mL)
L = label claim (mg/Capsule)
V = volume of *Medium*, 900 mL
D = dilution factor for the *Sample solution*, if applicable

Tolerances: NLT 80% (Q) of the labeled amount of itraconazole ($C_{35}H_{38}Cl_2N_8O_4$) is dissolved.

▲Test 2: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*. All solutions containing itraconazole should be stored in low-actinic or amber glassware and protected from light.
Medium: Simulated gastric fluid without enzymes, deaerated; 900 mL
Apparatus 2: 100 rpm; with a sinker
Time: 60 min
Standard stock solution: 0.55 mg/mL of USP Itraconazole RS in methanol prepared as follows. Transfer suitable amount of USP Itraconazole RS to a suitable volumetric flask and add about 80% of the flask volume of methanol. Heat the solution to 65° in a water bath, with intermittent stirring, until dissolved. Dilute with methanol to final volume.
Standard solution: 0.022 mg/mL of USP Itraconazole RS in *Medium* from *Standard stock solution*
Sample solution: Pass a portion of the solution under test through a suitable filter and dilute with *Medium*, if necessary.
Blank: *Medium*
Instrumental conditions
Mode: UV

Analytical wavelength: 255 nm
System suitability
Sample: *Standard solution*
Suitability requirements
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of itraconazole ($C_{35}H_{38}Cl_2N_8O_4$) dissolved:

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

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of USP Itraconazole RS in the *Standard solution* (mg/mL)
L = label claim (mg/Capsule)
V = volume of *Medium*, 900 mL
D = dilution factor for the *Sample solution*, if applicable

Tolerances: NLT 80% (Q) of the labeled amount of itraconazole ($C_{35}H_{38}Cl_2N_8O_4$) is dissolved.▲ (RB 1-Aug-2019)

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

IMPURITIES

Change to read:

• **Organic Impurities**
Solution A, Solution B, and **Diluent:** Prepare as directed in the *Assay*.
Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	60	40
25	45	55
40	45	55
42	60	40
50	60	40

System suitability solution: 5 mg/mL of USP Itraconazole System Suitability Mixture RS in *Diluent*. Sonicate, if necessary, to dissolve.
Standard solution: 0.025 mg/mL of USP Itraconazole RS in *Diluent*. Sonicate, if necessary, to dissolve.
Sample solution: Nominally 5 mg/mL of itraconazole in *Diluent* prepared as follows. Combine the contents of NLT 20 Capsules and transfer a portion nominally equivalent to 500 mg of itraconazole to a 100-mL flask. Add about 70 mL of *Diluent* and sonicate for 30 min with intermittent shaking. Dilute with *Diluent* to volume. Pass through a suitable filter of 0.45-µm pore size.
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 225 nm
Column: 4.6-mm × 15-cm; 3-µm packing L1
Column temperature: 30°
Flow rate: 1.5 mL/min
Injection volume: 10 µL
System suitability
Samples: *System suitability solution* and *Standard solution*
[NOTE—See *Table 2* for relative retention times.]
Suitability requirements
Resolution: NLT 1.5 between itraconazole and *n*-butyl isomer, *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 any individual impurity in the portion of Capsules taken:

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

r_U = peak response of any individual impurity from the *Sample solution*
r_S = peak response of itraconazole from the *Standard solution*
C_S = concentration of USP Itraconazole RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of itraconazole in the *Sample solution* (mg/mL)

Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	▲ (RB 1-Aug-2019)	Acceptance Criteria, NMT (%)
4-Methoxy derivative[a, b]	0.28	▲ (RB 1-Aug-2019)	—
4-Triazolyl isomer[b, c]	0.64	▲ (RB 1-Aug-2019)	—
Propyl and isopropyl analog[b, d, e]	0.77	▲ (RB 1-Aug-2019)	—
Epimer[b, f]	0.84	▲ (RB 1-Aug-2019)	—
Itraconazole	1.0	▲ (RB 1-Aug-2019)	—
n-Butyl isomer[b, g]	1.1	▲ (RB 1-Aug-2019)	—
Didioxolanyl analog[b, h]	1.4	▲ (RB 1-Aug-2019)	—
Any individual unspecified impurity	—	▲ (RB 1-Aug-2019)	0.2

Table 2 *(continued)*

Name	Relative Retention Time	▲▲ (RB 1-Aug-2019)	Acceptance Criteria, NMT (%)
Total impurities	—	▲▲ (RB 1-Aug-2019)	1.50

[a] 2-*sec*-Butyl-4-{4-[4-(4-methoxyphenyl)piperazin-1-yl]phenyl}-2*H*-1,2,4-triazol-3(4*H*)-one.

[b] Process-related impurity ▲included in the table for identification only. Process-related impurities are▲ (RB 1-Aug-2019) controlled in the drug substance▲ and are not to be reported or included in the total impurities of the drug product.▲ (RB 1-Aug-2019)

[c] 4-(4-{4-[4-({(2*RS*,4*SR*)-2-[(4*H*-1,2,4-Triazol-4-yl)methyl]-2-(2,4-dichlorophenyl)-1,3-dioxolan-4-yl}methoxy)phenyl]piperazin-1-yl}phenyl)-2-*sec*-butyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one.

[d] 4-(4-{4-[4-({(2*RS*,4*SR*)-2-[(1*H*-1,2,4-Triazol-1-yl)methyl]-2-(2,4-dichlorophenyl)-1,3-dioxolan-4-yl}methoxy)phenyl]piperazin-1-yl}phenyl)-2-propyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one.

[e] 4-(4-{4-[4-({(2*RS*,4*SR*)-2-[(1*H*-1,2,4-Triazol-1-yl)methyl]-2-(2,4-dichlorophenyl)-1,3-dioxolan-4-yl}methoxy)phenyl]piperazin-1-yl}phenyl)-2-isopropyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one.

[f] 4-(4-{4-[4-({(2*RS*,4*RS*)-2-[(1*H*-1,2,4-Triazol-1-yl)methyl]-2-(2,4-dichlorophenyl)-1,3-dioxolan-4-yl}methoxy)phenyl]piperazin-1-yl}phenyl)-2-*sec*-butyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one.

[g] 4-(4-{4-[4-({(2*RS*,4*SR*)-2-[(1*H*-1,2,4-Triazol-1-yl)methyl]-2-(2,4-dichlorophenyl)-1,3-dioxolan-4-yl}methoxy)phenyl]piperazin-1-yl}phenyl)-2-butyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one.

[h] Mixture of 4-(4-{4-[4-({(2*RS*,4*SR*)-2-[(1*H*-1,2,4-Triazol-1-yl)methyl]-2-(2,4-dichlorophenyl)-1,3-dioxolan-4-yl}methoxy)phenyl]piperazin-1-yl}phenyl)-2-({(2*RS*,4*SR*)-2-[(1*H*-1,2,4-triazol-1-yl)methyl]-2-(2,4-dichlorophenyl)-1,3-dioxolan-4-yl}methyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one and 4-(4-{4-[4-({(2*RS*,4*SR*)-2-[(1*H*-1,2,4-Triazol-1-yl)methyl]-2-(2,4-dichlorophenyl)-1,3-dioxolan-4-yl}methoxy)phenyl]piperazin-1-yl}phenyl)-2-({(2*SR*,4*RS*)-2-[(1*H*-1,2,4-triazol-1-yl)methyl]-2-(2,4-dichlorophenyl)-1,3-dioxolan-4-yl}methyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers. 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.▲ (RB 1-Aug-2019)

- **USP REFERENCE STANDARDS** ⟨11⟩
  USP Itraconazole RS
  USP Itraconazole System Suitability Mixture RS
  This is a mixture of itraconazole, 4-triazolyl isomer, propyl analog, epimer, *n*-butyl isomer, and didioxolanyl analog (other impurities may also be present).▲ USP 1-Aug-2019