## Itraconazole Capsules

<table>
<thead>
<tr>
<th>Type of Posting</th>
<th>Revision Bulletin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posting Date</td>
<td>31–May–2019</td>
</tr>
<tr>
<td>Official Date</td>
<td>01–August–2019</td>
</tr>
<tr>
<td>Expert Committee</td>
<td>Chemical Medicines Monographs 1</td>
</tr>
<tr>
<td>Reason for Revision</td>
<td>Compliance</td>
</tr>
</tbody>
</table>

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$_{15}$H$_{18}$Cl$_2$N$_4$O$_5$).

**APPLICATION**

**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 solution:** Nominally 0.1 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

**Suitability requirements**
Sample: Standard solution
  **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$_{15}$H$_{18}$Cl$_2$N$_4$O$_5$) released:

\[
\text{Result} = \left( \frac{A_u}{A_s} \right) \times \left( \frac{C_s}{C_u} \right) \times \frac{V}{D} \times 100
\]

\[A_u = \text{absorbance of the Sample solution}\]
\[A_s = \text{absorbance of the Standard solution}\]
\[C_s = \text{concentration of USP Itraconazole RS in the Standard solution (mg/mL)}\]
\[C_u = \text{nominal concentration of itraconazole in the Sample solution (mg/mL)}\]

**Acceptance criteria:** 90.0%–110.0%

**PERFORMANCE TESTS**

**Change to read:**

• **Dissolution (711)**
  **Test 1 a** (81-1-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$_{15}$H$_{18}$Cl$_2$N$_4$O$_5$) released:

\[
\text{Result} = \left( \frac{A_u}{A_s} \right) \times \left( \frac{C_s}{C_u} \right) \times \frac{V}{D} \times 100
\]

\[A_u = \text{absorbance of the Sample solution}\]
\[A_s = \text{absorbance of the Standard solution}\]
\[C_s = \text{concentration of USP Itraconazole RS in the Standard solution (mg/mL)}\]
\[C_u = \text{nominal concentration of itraconazole in the Sample solution (mg/mL)}\]

**Acceptance criteria:** NLT 80.0% (Q) of the labeled amount of itraconazole (C$_{15}$H$_{18}$Cl$_2$N$_4$O$_5$) 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

---

© 2019 The United States Pharmacopeial Convention All Rights Reserved.

C202266-M43726-CHM12015 rev. 00 20190531
2 Itraconazole

[Nota—See Table 2 for relative retention times.]

**Suitability requirements**

**Resolution:** NLT 1.5 between itraconazole and n-butyl isomer, System suitability solution

**Tailing factor:** NLT 10.0, Standard solution

**Relative standard deviation:** NMT 2.0, Standard solution

**Analysis**

**Samples:** Standard solution and Sample solution

Calculate the percentage of any individual impurity in the portion of Capsules taken:

\[
\text{Result} = \left( \frac{r_u}{r_s} \right) \times \left( \frac{C_s}{C_u} \right) \times 100
\]

**Acceptance criteria:** See Table 2.

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-Methoxy derivative (_1^b)</td>
<td>0.28</td>
<td>(\leq 0.5) (RB 1-Aug-2019)</td>
</tr>
<tr>
<td>4-Triazolyl isomer (_1^b)</td>
<td>0.64</td>
<td>(\leq 0.5) (RB 1-Aug-2019)</td>
</tr>
<tr>
<td>Propyl and isopropyl analog (_1^b)</td>
<td>0.77</td>
<td>(\leq 1) (RB 1-Aug-2019)</td>
</tr>
<tr>
<td>Epimer (_1^b)</td>
<td>0.84</td>
<td>(\leq 0.5) (RB 1-Aug-2019)</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>1.0</td>
<td>(\leq 0.5) (RB 1-Aug-2019)</td>
</tr>
<tr>
<td>n-Butyl isomer (_1^b)</td>
<td>1.1</td>
<td>(\leq 0.5) (RB 1-Aug-2019)</td>
</tr>
<tr>
<td>Didoxolanyl analog (_1^b)</td>
<td>1.4</td>
<td>(\leq 0.5) (RB 1-Aug-2019)</td>
</tr>
<tr>
<td>Any individual unspecified impurity</td>
<td>—</td>
<td>(\leq 0.5) (RB 1-Aug-2019)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 1</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (min)</td>
<td>Solution A (%)</td>
</tr>
<tr>
<td>0</td>
<td>60</td>
</tr>
<tr>
<td>25</td>
<td>45</td>
</tr>
<tr>
<td>40</td>
<td>45</td>
</tr>
<tr>
<td>42</td>
<td>60</td>
</tr>
<tr>
<td>50</td>
<td>60</td>
</tr>
</tbody>
</table>

**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

**Tolerances:** NLT 80% (Q) of the labeled amount of itraconazole (C\(_{13}\)H\(_{15}\)Cl\(_2\)N\(_3\)O\(_4\)) is dissolved.

- **Uniformity of Dosage Units (905):** Meet the requirements

**IMPUlILITIES**

**Change to read:**

- **Organic impurities**

  Solution A, Solution B, and Diluent: Prepare as directed in the Assay.

  **Mobile phase:** See Table 1.
<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total impurities</td>
<td>—</td>
<td>1.50</td>
</tr>
</tbody>
</table>

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

\[b\] Process-related impurity \* included in the table for identification only.

\[c\] 4-(4-[[4-[(2RS,4SR)-2-(4H-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-3H-1,2,4-triazol-3-one.

\[d\] 4-(4-[[4-[(2RS,4SR)-2-(1H-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-3H-1,2,4-triazol-3-one.

\[e\] 4-(4-[[4-[(2RS,4SR)-2-(1H-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-3H-1,2,4-triazol-3-one.

\[f\] 4-(4-[[4-[[4-[(2RS,4SR)-2-(1H-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-3H-1,2,4-triazol-3-one.

\[g\] 4-(4-[[4-[[4-[(2RS,4RS)-2-(1H-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-3H-1,2,4-triazol-3-one.

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

**• 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).