Indomethacin Suppositories

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<th>Type of Posting</th>
<th>Revision Bulletin</th>
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<td>22–Nov–2019</td>
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<td>Official Date</td>
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<tr>
<td>Expert Committee</td>
<td>Chemical Medicines Monographs 2</td>
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In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Chemical Medicines Monographs 2 Expert Committee has revised the Indomethacin Suppositories monograph. The purpose of this revision is to delete the *Organic Impurities* test, in which the procedure is not suitable for the analysis of the only marketed product approved by the FDA and the *Acceptance criteria* are not consistent with the FDA-approved specifications. USP intends to publish an additional revision proposal in the *Pharmacopeial Forum* to add an *Organic Impurities* test to be consistent with the FDA-approved applications.

The Indomethacin Suppositories Revision Bulletin supersedes the currently official Indomethacin Suppositories monograph.

Should you have any questions, please contact Wei Yang, Scientific Liaison (301-816-8338 or wiy@usp.org).
Indomethacin Suppositories

DEFINITION
Indomethacin Suppositories contain NLT 90.0% and NMT 110.0% of the labeled amount of indomethacin (C_{18}H_{20}CINO_{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 indomethacin peak of the Sample solution corresponds to that of the Standard solution, as obtained in the Assay.

ASSAY
• PROCEDURE
Solution A: Prepare 0.1% of formic acid by diluting 1 mL of formic acid with water to 1 L.
Mobile phase: Acetonitrile and Solution A (45:55)
Diluent: Mobile phase adjusted with 0.2 M sodium hydroxide (NaOH) to a pH of 8.0
System suitability solution: 0.002 mg/mL of USP Indomethacin RS in Diluent
Related Compound A RS, and 0.01 mg/mL of USP Indomethacin Related Compound B RS in Diluent
Standard solution: 0.5 mg/mL of USP Indomethacin RS in Diluent
Sample solution: Prepare a solution nominally equivalent to 0.5 mg/mL of indomethacin in Diluent as follows. Mash NLT 10 Suppositories in a beaker, and heat (at about 50°) on a water bath until melted. Mix well and cool. Transfer a portion of the mass equivalent to 10 mg of indomethacin into a 20-mL volumetric flask and add 10 mL of acetonitrile. Heat in a water bath at 50° to dissolve, and dilute with Diluent to volume.

Chromatographic system
(See Chromatography (621), System Suitability.)
Mode: LC
Detector: PDA (scan 200–600). Calculations should be based on the chromatograms collected at 240 nm. For Identification test B, use spectra at the scanned range.
Column: 4.6-mm × 25-cm; 5-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
Suitability requirements
Resolution: NLT 4 between indomethacin related compound A and indomethacin related compound B, System suitability solution
Tailing factor: NMT 1.5, Standard solution
Relative standard deviation: NMT 1.0%, Standard solution
Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of the labeled amount of indomethacin (C_{18}H_{20}CINO_{4}) in the Suppository taken:
Result = \( \left( \frac{A_1}{A_0} \right) \times \left( \frac{C_3}{C_0} \right) \times 100 \)

• IMPURITIES

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS
• DISSOLUTION (711)
Medium: 0.1 M, pH 7.2 phosphate buffer (see Reagents, Indicators, and Solutions—Buffer Solutions); 900 mL
Apparatus 2: 50 rpm
Time: 60 min
Standard solution: USP Indomethacin RS at a known concentration in Medium
Sample solution: Proceed as directed for sample per Dissolution (711). Dilute with Medium as needed.
Instrumental conditions
Mode: UV
Analytical wavelength: 320 nm
Analysis
Samples: Standard solution and Sample solution
Tolerances: NLT 75% (Q) of the labeled amount of indomethacin (C_{18}H_{20}CINO_{4}) is dissolved.

• UNIFORMITY OF DOSAGE UNITS (905)
Diluent: Methanol and glacial acetic acid (199:1)
Standard solution: 25 µg/mL of USP Indomethacin RS in Diluent
Sample solution: Place 1 Suppository into a 100-mL volumetric flask containing 80 mL of Diluent, shake by mechanical means until the Suppository is dissolved, and dilute with Diluent to volume. Filter a portion of the solution, discarding the first 15 mL of the filtrate, and dilute a volume of the clear filtrate with the Diluent to obtain a solution having a concentration of 25 µg/mL of indomethacin.

Instrumental conditions
Mode: UV
Detector: 320 nm
Blank: Diluent
Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of the labeled amount of indomethacin (C_{18}H_{20}CINO_{4}) in the Suppository taken:
Result = \( \left( \frac{A_1}{A_0} \right) \times \left( \frac{C_3}{C_0} \right) \times 100 \)

Acceptance criteria: Meet the requirements in Uniformity of Dosage Units (905)

IMPURITIES

Delete the following:

• ORGANIC IMPURITIES

Mobile phase, Diluent, and Chromatographic system: Proceed as directed in the Assay.
Standard solution: 0.002 mg/mL of USP Indomethacin RS, 0.002 mg/mL of USP Indomethacin Related Compound A RS, and 0.01 mg/mL of USP Indomethacin Related Compound B RS in Diluent
Sample solution: Prepare a solution nominally equivalent to 2.0 mg/mL of indomethacin in Diluent as follows. Mash NLT 10 Suppositories in a beaker, and heat (at about 50°) on a water bath until melted. Mix well and cool. Transfer a portion of the mass equivalent to 40 mg of indomethacin into a 20-mL volumetric flask and add 10 mL of acetonitrile.
Heat in a water bath at 50° to dissolve, and dilute with Diluent to volume.

System suitability

**Sample:** Standard solution

[NOTE—See Table 1 for the relative retention times.]

**Suitability requirements**

**Resolution:** NLT 4 between indomethacin related compound A and indomethacin related compound B

**Relative standard deviation:** NMT 2.8%

**Analysis**

**Samples:** Standard solution and Sample solution

Calculate the percentage of indomethacin related compound A and indomethacin related compound B in the portion of Suppositories taken:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times 100
\]

\(r_U\) = peak response of indomethacin related compound A or indomethacin related compound B from the Sample solution

\(r_S\) = peak response of indomethacin related compound A or indomethacin related compound B from the Standard solution

\(C_S\) = concentration of the corresponding USP Indomethacin Related Compound A RS or USP Indomethacin Related Compound B RS in the Standard solution (mg/mL)

\(C_U\) = nominal concentration of indomethacin in the Sample solution (mg/mL)

Calculate the percentage of any unspecified impurity in the portion of Suppositories taken:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times 100
\]

\(r_U\) = peak response of unspecified impurity from the Sample solution

\(r_S\) = peak response of indomethacin from the Standard solution

\(C_S\) = concentration of USP Indomethacin RS in the Standard solution (mg/mL)

\(C_U\) = nominal concentration of indomethacin in the Sample solution (mg/mL)

**Acceptance criteria:** See Table 1. Disregard any impurity peak less than 0.05%.

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria, NMT (%)</th>
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<tbody>
<tr>
<td>Indomethacin related compound A</td>
<td>0.15</td>
<td>0.1</td>
</tr>
<tr>
<td>Indomethacin related compound B</td>
<td>0.25</td>
<td>0.5</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Any other individual, unidentified impurity</td>
<td>=</td>
<td>0.1</td>
</tr>
<tr>
<td>Total impurities</td>
<td>=</td>
<td>2.0 ➤ (RB 1-Dec-2019)</td>
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**ADDITIONAL REQUIREMENTS**

- **Packaging and Storage:** Preserve in well-closed containers at controlled room temperature.
- **USP Reference Standards**

USP Indomethacin RS

USP Indomethacin Related Compound A RS
5-Methoxy-2-methyl-3-indoleacetic acid.
\(\text{C}_{12}\text{H}_{13}\text{NO}_3\) 219.24

USP Indomethacin Related Compound B RS
4-Chlorobenzoic acid.
\(\text{C}_7\text{H}_5\text{ClO}_2\) 156.57