Torsemide Tablets

Type of Posting: Notice of Intent to Revise
Posting Date: 26-Jan-2024
Targeted Official Date: To Be Determined, Revision Bulletin
Expert Committee: Small Molecules 2

In accordance with the Rules and Procedures of the Council of Experts and the Pending Monograph Guideline, this is to provide notice that the Small Molecules 2 Expert Committee intends to revise the Torsemide Tablets monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to revise the Torsemide Tablets monograph to add Dissolution Test 3.

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 Yanyin Yang, Senior Scientist II (301-692-3623 or yanyin.yang@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.
Torsemide Tablets

**DEFINITION**
Torsemide Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of torsemide ($\text{C}_{16}\text{H}_{20}\text{N}_{4}\text{O}_{3}\text{S}$).

**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**
  - **Buffer:** 2.72 g/L of monobasic potassium phosphate
  - **Solution A:** Acetonitrile and methanol (10:90)
  - **Mobile phase:** Buffer and Solution A (50:50). Adjust with diluted phosphoric acid (1 in 10 v/v) to a pH of 4.0.
  - **Standard solution:** 0.4 mg/mL of USP Torsemide RS prepared as follows. To a quantity of USP Torsemide RS in a suitable flask, add methanol to 30% of the flask volume and sonicate for NLT 8 min. Add Buffer to fill 75% of the flask volume, cool, and dilute with Mobile phase. Pass through a membrane filter of 0.45-µm pore size.
  - **Sample solution:** Nominally 0.4 mg/mL of torsemide prepared as follows. Place 40 mg of torsemide from NLT 20 powdered Tablets in a 100-mL volumetric flask. Add methanol to 30% of the flask volume and sonicate for NLT 8 min. Add Buffer to fill 75% of the flask volume, cool, and dilute with Mobile phase. Pass through a membrane filter of 0.45-µm pore size. The Sample solution is not stable at room temperature but is stable for 12 h at 6°.

**Chromatographic system**
(See Chromatography (621), System Suitability.)
- **Mode:** LC
- **Detector:** UV 288 nm. For Identification B, use a diode array detector in the range of 200–400 nm.
- **Column:** 4.6-mm × 15-cm; 5-µm packing L1
- **Temperatures**
  - **Autosampler:** 6°
  - **Column:** 30°
- **Flow rate:** 1 mL/min
- **Injection volume:** 20 µL
- **Run time:** NLT 2 times the retention time of torsemide

**System suitability**
- **Sample:** Standard solution
- **Suitability requirements**
  - **Tailing factor:** NMT 1.5
Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of torsemide \((C_{16}H_{20}N_4O_3S)\) in the portion of Tablets 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 torsemide from the *Sample solution*
- \(r_S\) = peak response of torsemide from the *Standard solution*
- \(C_S\) = concentration of USP Torsemide RS in the *Standard solution* (mg/mL)
- \(C_U\) = nominal concentration of torsemide in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

*Change to read:*

- **Dissolution** (711)

**Test 1**

Medium: 0.1 N hydrochloric acid; 900 mL

Apparatus 2: 50 rpm

Time: 15 min

Buffer, Mobile phase, Chromatographic system, and System suitability: Proceed as directed in the Assay.

**Standard stock solution:** 0.55 mg/mL of USP Torsemide RS prepared as follows. Transfer a quantity of USP Torsemide RS to a suitable volumetric flask. Add methanol to 30% of the flask volume and sonicate until dissolved. Add Buffer to fill 75% of the flask volume, cool to room temperature, and dilute with Mobile phase to volume.

**Standard solution:** Dilute the Standard stock solution with Medium to obtain a final concentration of \((L/900)\) mg/mL, where \(L\) is the label claim in mg/Tablet.

**Sample solution:** Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size.

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of torsemide \((C_{16}H_{20}N_4O_3S)\) dissolved:

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

- \(r_U\) = peak response of torsemide from the *Sample solution*
- \(r_S\) = peak response of torsemide from the *Standard solution*
- \(C_S\) = concentration of USP Torsemide RS in the *Standard solution* (mg/mL)
- \(L\) = label claim (mg/Tablet)
- \(V\) = volume of Medium, 900 mL

Tolerances: NLT 80% \((Q)\) of the labeled amount of torsemide \((C_{16}H_{20}N_4O_3S)\) is dissolved.

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

Medium: 0.1 N hydrochloric acid; 900 mL
Apparatus 2: 50 rpm
Time: 30 min

Standard stock solution: 0.11 mg/mL of USP Torsemide RS in Medium

Standard solution: Dilute the Standard stock solution with Medium to obtain a final concentration of \((L/900)\) mg/mL, where \(L\) is the label claim in mg/Tablet.

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

Instrumental conditions
(See Ultraviolet-Visible Spectroscopy (857).)

Mode: UV
Analytical wavelength: 285 nm
Cell: 1.0 cm for 5-, 10-, and 20-mg Tablets and 0.1 cm for 100-mg Tablets
Blank: Medium

Analysis

Samples: Standard solution and Sample solution

Calculate the percentage of the labeled amount of torsemide \((C_{16}H_{20}N_{4}O_{3}S)\) dissolved:

\[
\text{Result} = \left(\frac{A_U}{A_S}\right) \times \left(\frac{C_S}{L}\right) \times V \times 100
\]

\(A_U\) = absorbance of the Sample solution
\(A_S\) = absorbance of the Standard solution
\(C_S\) = concentration of USP Torsemide RS in the Standard solution (mg/mL)
\(L\) = label claim (mg/Tablet)
\(V\) = volume of Medium, 900 mL

Tolerances: NLT 80% \((Q)\) of the labeled amount of torsemide \((C_{16}H_{20}N_{4}O_{3}S)\) is dissolved.

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

Medium: 0.1 N hydrochloric acid; 500 mL
Apparatus 2: 50 rpm
Time: 15 min

Solution A: Acetonitrile and methanol (10:90)

Solution B: Dissolve 2.72 g of monobasic potassium phosphate in 1000 mL of water.

Solution C: Dilute 10 mL of phosphoric acid with water to 100 mL.


Standard stock solution: 0.56 mg/mL of USP Torsemide RS in methanol. Sonicate to dissolve, if necessary.

Standard solution: \((L/500)\) mg/mL of USP Torsemide RS from the Standard stock solution in Medium, where \(L\) is the label claim in mg/Tablet

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size, discarding an appropriate volume of filtrate so that a consistent result can be obtained.

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: 30°
Flow rate: 1 mL/min
Injection volume: 20 µL
Run time: NLT 1.5 times the retention time of torsemide

System suitability
Sample: Standard solution
Suitability requirements
Tailing factor: NMT 1.5
Relative standard deviation: NMT 2.0%

Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of the labeled amount of torsemide \((C_{16}H_{20}N_{4}O_{3}S)\) dissolved:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times C_S \times V \times \left( \frac{1}{L} \right) \times 100
\]

- \(r_U\) = peak response of torsemide from the Sample solution
- \(r_S\) = peak response of torsemide from the Standard solution
- \(C_S\) = concentration of USP Torsemide RS in the Standard solution (mg/mL)
- \(V\) = volume of Medium, 500 mL
- \(L\) = label claim (mg/Tablet)

Tolerances: NLT 80% (Q) of the labeled amount of torsemide \((C_{16}H_{20}N_{4}O_{3}S)\) is dissolved

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

**Impurities**

- **Organic Impurities**
  - Buffer and Solution A: Prepare as directed in the Assay.
  - Mobile phase: Buffer and Solution A (55:45). Adjust with diluted phosphoric acid (1 in 10 v/v) to a pH of 4.0.

Standard stock solution A: 0.1 mg/mL of USP Torsemide Related Compound A RS and 0.02 mg/mL of USP Torsemide Related Compound E RS prepared as follows. Dissolve a suitable quantity each of USP Torsemide Related Compound A RS and USP Torsemide Related Compound E RS in methanol to 32% of the flask volume and sonicate to dissolve. Dilute with Mobile phase to volume.

System suitability solution: 0.4 mg/mL of USP Torsemide RS, 4 µg/mL of USP Torsemide Related Compound A RS, and 0.8 µg/mL of USP Torsemide Related Compound E RS prepared as follows. To a quantity of USP Torsemide RS in a suitable flask add methanol to 30% of the flask volume and sonicate to dissolve. Add Buffer to fill 75% of the flask volume, and cool. Add a suitable volume of Standard stock solution A and dilute with Mobile phase to volume.

Standard stock solution B: 0.4 mg/mL each of USP Torsemide RS prepared as follows. To a suitable amount of USP Torsemide RS in a suitable flask, add methanol to 30% of the flask volume and sonicate for NLT 8 min. Add Buffer to fill 75% of the flask volume, cool, and dilute with Mobile phase to volume.

Sensitivity solution: 0.4 µg/mL of USP Torsemide RS in Mobile phase from Standard stock solution B

Standard solution: 4 µg/mL each of USP Torsemide RS and USP Torsemide Related Compound A RS and 0.8 µg/mL of USP Torsemide Related Compound E RS in Mobile phase from Standard stock solution A and Standard stock solution B
Sample solution: Nominally 0.4 mg/mL of torsemide prepared as follows. Weigh 40 mg of torsemide from NLT 20 powdered Tablets into a 100-mL volumetric flask. Add methanol to 30% of the flask volume, mix, and sonicate for NLT 8 min. Add Buffer to fill 75% of the flask volume, cool to room temperature, dilute with Mobile phase to volume, and mix. The Sample solution is not stable at room temperature, but is stable for 15 h at 6°.

Chromatographic system
(See Chromatography (621), System Suitability.)

Mode: LC
Detector: UV 288 nm
Column: 4.6-mm × 15-cm; 3.5-µm packing L1
Autosampler temperature: 6°
Flow rate: 0.8 mL/min
Injection volume: 20 µL

System suitability

Samples: System suitability solution, Sensitivity solution, and Standard solution

[Note—See Table 1 for relative retention times.]

Suitability requirements

Resolution: NLT 2.5 between torsemide related compound A and torsemide related compound E, System suitability solution
Tailing factor: NMT 2.0 for the torsemide peak, System suitability solution
Relative standard deviation: NMT 5.0% for the torsemide peak, Standard solution
Signal-to-noise ratio: NLT 10.0, Sensitivity solution

Analysis

Samples: Standard solution and Sample solution
Calculate the percentage of torsemide related compound A or torsemide related compound E in the portion of Tablets 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 torsemide related compound A or torsemide related compound E from the Sample solution
\(r_S\) = peak response of torsemide related compound A or torsemide related compound E from the Standard solution
\(C_S\) = concentration of USP Torsemide Related Compound A RS or USP Torsemide Related Compound E RS in the Standard solution (mg/mL)
\(C_U\) = nominal concentration of torsemide in the Sample solution (mg/mL)

Calculate the percentage of any unspecified degradation product in the portion of Tablets 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 any unspecified degradation product from the Sample solution
\(r_S\) = peak response of torsemide from the Standard solution
\(C_S\) = concentration of USP Torsemide RS in the Standard solution (mg/mL)
\(C_U\) = nominal concentration of torsemide in the Sample solution (mg/mL)
Acceptance criteria: See Table 1.

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Torsemide related compound A</td>
<td>0.39</td>
<td>0.6</td>
</tr>
<tr>
<td>Torsemide related compound E</td>
<td>0.50</td>
<td>0.3</td>
</tr>
<tr>
<td>Torsemide related compound C&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>0.62</td>
<td>—</td>
</tr>
<tr>
<td>Torsemide related compound D&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>0.75</td>
<td>—</td>
</tr>
<tr>
<td>Torsemide</td>
<td>1.00</td>
<td>—</td>
</tr>
<tr>
<td>Torsemide related compound B&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1.96</td>
<td>—</td>
</tr>
<tr>
<td>Any unspecified degradation product</td>
<td>—</td>
<td>0.2</td>
</tr>
<tr>
<td>Total impurities</td>
<td>—</td>
<td>1.1</td>
</tr>
</tbody>
</table>

<sup>a</sup> N-(Ethylcarbamoyl)-4-(3-tolylamino)pyridine-3-sulfonamide.

<sup>b</sup> Process-related impurity controlled in the drug substance.

<sup>c</sup> Ethyl \{4-(3-tolylamino)pyridin-3-yl\}sulfonylcarbamate.

<sup>d</sup> N-(Butylcarbamoyl)-4-(3-tolylamino)pyridine-3-sulfonamide.

**ADDITIONAL REQUIREMENTS**

- **Packaging and Storage:** Preserve in tight containers and store at controlled room temperature.

- **Labeling:** The labeling indicates the *Dissolution* test with which the product complies, if *Test 1* is not used.

- **USP Reference Standards** ([11])

  **USP Torsemide RS**

  **USP Torsemide Related Compound A RS**

  4-[[3-Methylphenyl]amino]-3-pyridinesulfonamide.

  \[C_{12}H_{13}N_3O_2S\] 263.32

  **USP Torsemide Related Compound E RS**

  4-(3-Tolyl)-2H-pyrido[4,3-e][1,2,4]thiadiazin-3(4H)-one 1,1-dioxide.

  \[C_{13}H_{11}N_3O_3S\] 289.31