



## Torsemid Tablets

<b>Type of Posting</b>	Notice of Intent to Revise
<b>Posting Date</b>	26-Jan-2024
<b>Targeted Official Date</b>	To Be Determined, Revision Bulletin
<b>Expert Committee</b>	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.<sup>1</sup>

Should you have any questions, please contact Yanyin Yang, Senior Scientist II (301-692-3623 or [yanyin.yang@usp.org](mailto:yanyin.yang@usp.org)).

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<sup>1</sup> 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 ( $C_{16}H_{20}N_4O_3S$ ).

### 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- $\mu$ m 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- $\mu$ m 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  $\times$  15-cm; 5- $\mu$ m packing [L1](#)

#### Temperatures

**Autosampler:** 6°

**Column:** 30°

**Flow rate:** 1 mL/min

**Injection volume:** 20  $\mu$ L

**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:

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

$r_U$  = 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- $\mu$ m 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:

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

$r_U$  = 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 ( $C_{16}H_{20}N_4O_3S$ ) dissolved:

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

$A_U$  = 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 ( $C_{16}H_{20}N_4O_3S$ ) 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.

**Mobile phase:** *Solution A* and *Solution B* (50:50). Adjust with *Solution C* to a pH of 4.0.

**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- $\mu$ m 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  $\times$  15-cm; 5- $\mu$ m 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 ( $C_{16}H_{20}N_4O_3S$ ) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (1/L) \times 100$$

$r_U$  = 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 ( $C_{16}H_{20}N_4O_3S$ ) is dissolved ▲ (TBD)

- **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:

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

$r_U$  = 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:

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

$r_U$  = 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 1**

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

<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]sulfonyl}carbamate.

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

$C_{13}H_{11}N_3O_3S$  289.31

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**Page Information:**

Not Applicable

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