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*.

ASSAY
• **PROCEDURE**
Buffer: 2.72 g/L of monobasic potassium phosphate. Pass through a suitable membrane filter of 0.45-µm pore size.
Solution A: Acetonitrile and methanol (10:90)
Mobile phase: *Solution A* and *Buffer* (50:50). Adjust with diluted (1 in 10 v/v) phosphoric acid 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 (30% of the volume of the flask), and sonicate for NLT 8 min. Add *Buffer* to fill 75% of the volume of the flask, 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 an amount equivalent to 40 mg from powdered Tablets (NLT 20) in a 100-mL volumetric flask. Initially add methanol (30% of the volume of the flask), and sonicate for NLT 8 min. Add *Buffer* to fill 75% of the volume of the flask, cool, and dilute with *Mobile phase*. Pass through a membrane filter of 0.45-µm pore size. [NOTE—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
Column: 4.6-mm × 15-cm; 5-µm packing L1
Column temperature: 30°
Flow rate: 1 mL/min
Injection volume: 20 µL
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 from the *Sample solution*
r_S = peak response 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
• **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 prepared as follows. Transfer a quantity of USP Torsemide RS to a suitable volumetric flask. Add methanol (30% of the volume of the flask), and sonicate until dissolved. Add *Buffer* to fill 75% of the volume of the flask, 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 Tablet label claim, in mg.
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:

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

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Torsemide RS in the *Standard solution* (mg/mL)
L = label claim (mg/Tablet)
D_S = dilution factor of the *Standard solution*
D_U = dilution factor of the *Sample solution*
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 Tablet label claim, in mg.
Sample solution: Pass a portion of the solution under test through a suitable filter.
Instrumental conditions
(See *Spectrophotometry and Light-Scattering* ⟨851⟩.)
Mode: UV
Analytical wavelength: 285 nm
Cell length: 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.

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

IMPURITIES

Change to read:

- **Organic Impurities**

Buffer and Solution A: Proceed as directed in the *Assay*.

Mobile phase: *Solution A* and *Buffer* (45:55). Adjust with diluted (1 in 10 v/v) phosphoric acid to a pH of 4.0.

System suitability stock solution: 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 (about 32% of the volume of the flask), and sonicate to dissolve. Dilute with *Mobile phase* to volume.

System suitability solution: 4 µg/mL of USP Torsemide Related Compound A RS and 0.8 µg/mL of USP Torsemide Related Compound E RS in *Mobile phase*

Standard stock solution: 0.4 mg/mL each of USP Torsemide RS and USP Torsemide Related Compound A RS and 0.08 mg/mL of USP Torsemide Related Compound E RS prepared as follows. To a suitable amount of USP Torsemide RS, USP Torsemide Related Compound A RS, and USP Torsemide Related Compound E RS in a suitable flask add methanol (30% of the volume of the flask), and sonicate for NLT 8 min. Add *Buffer* to fill 75% of the volume of the flask, cool, and dilute with *Mobile phase*.

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 the *Standard stock solution*

Sample solution: Nominally 0.4 mg/mL of USP Torsemide RS prepared as follows. Weigh 40 mg of torsemide from powdered Tablets (NLT 20) into a 100-mL volumetric flask. Add methanol (about 30% of the volume of the flask), mix, and sonicate for NLT 8 min. Add *Buffer* to fill 75% of the volume of the flask, cool to room temperature, dilute with *Mobile phase* to volume, and mix. [Note—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

Flow rate: 0.8 mL/min

Injection volume: 20 µL

System suitability

Samples: *System suitability solution* and *Standard solution*

Suitability requirements

Resolution: NLT 2.5 between torsemide related compound A and torsemide related compound E, *System suitability solution*

Tailing factor: NMT 2.0, *Standard solution*

Relative standard deviation: NMT 5.0%, *Standard 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 other individual impurity 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 individual impurity 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[a]	0.39	●0.6● (RB 1-Aug-2014)
Torsemide related compound E[b]	0.50	●0.3● (RB 1-Aug-2014)
Torsemide related compound C[c,d]	0.62	—
Torsemide impurity D[d,e]	0.75	—
Torsemide	1.00	—
Torsemide related compound B[d,f]	1.96	—
Any other unknown impurity	—	0.2
Total impurities	—	●1.1● (RB 1-Aug-2014)

[a] 4-[(3-Methylphenyl)amino]-3-pyridinesulfonamide.

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

[c] *N*-[(Ethylamino)carbonyl]-4-[(3-methylphenyl)amino]-3-pyridinesulfonamide.

[d] Process-related impurity and is controlled in the drug substance.

[e] Ethyl 4-(*m*-tolylamino)pyridin-3-ylsulfonylcarbamate.

[f] *N*-(*n*-Butylamino)carbonyl-4-[(3-methylphenyl)amino]-3-pyridinesulfonamide.

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**⟩ $C_{13}H_{11}N_3O_3S$ 289.31
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-*m*-Tolyl-2*H*-pyrido[4,3-*e*][1,2,4]thiadiazin-3(4*H*)-one 1,1-dioxide.