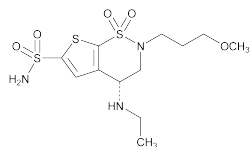


## Brinzolamide



$C_{12}H_{21}N_3O_5S_3$  383.51  
 2*H*-Thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide, 4-(ethylamino)-3,4-dihydro-2-(3-methoxypropyl)-, 1,1-dioxide, (*R*)-; (*R*)-4-(Ethylamino)-3,4-dihydro-2-(3-methoxypropyl)-2*H*-thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxide [138890-62-7].

### DEFINITION

Brinzolamide contains NLT 98.0% and NMT 102.0% of brinzolamide ( $C_{12}H_{21}N_3O_5S_3$ ), calculated on the dried basis.

### IDENTIFICATION

- A. INFRARED ABSORPTION** <197K>
- B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *System suitability solution*, as obtained in *Limit of Brinzolamide Related Compound A*.

### ASSAY

#### PROCEDURE

**Buffer:** Add 4.0 mL of triethylamine to 1000 mL of water, and adjust with phosphoric acid to a pH of 3.0.

**Mobile phase:** Acetonitrile and *Buffer* (25:75)

**Standard solution:** 0.1 mg/mL of USP Brinzolamide RS in *Mobile phase*

**Sample solution:** 0.1 mg/mL of Brinzolamide in *Mobile phase*

#### Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

**Mode:** LC

**Detector:** UV 254 nm

**Column:** 4.6-mm × 25-cm; 5-μm packing L1

**Flow rate:** 1.0 mL/min

**Injection volume:** 20 μL

#### System suitability

**Sample:** *Standard solution*

#### Suitability requirements

**Column efficiency:** NLT 1200 theoretical plates

**Tailing factor:** NMT 2.0

**Relative standard deviation:** NMT 2.0%

#### Analysis

**Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of brinzolamide ( $C_{12}H_{21}N_3O_5S_3$ ) in the portion of Brinzolamide 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 Brinzolamide RS in the *Standard solution* (mg/mL)

$C_U$  = concentration of Brinzolamide in the *Sample solution* (mg/mL)

**Acceptance criteria:** 98.0%–102.0% on the dried basis

### IMPURITIES

- RESIDUE ON IGNITION** <281>: NMT 0.1%

#### Delete the following:

- HEAVY METALS**, *Method II* <231>: NMT 20 ppm • (Official 1-

#### Change to read:

#### LIMIT OF BRINZOLAMIDE RELATED COMPOUND A

**Mobile phase:** Dehydrated alcohol, ▲chromatographic hexane, ▲USP38 methanol, and diethylamine (55: 40: 5: 0.2)

**System suitability solution:** 0.4 mg/mL of USP Brinzolamide RS and 0.02 mg/mL of USP Brinzolamide Related Compound A RS in dehydrated alcohol

**Sample solution:** 0.5 mg/mL of Brinzolamide in dehydrated alcohol

#### Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

**Mode:** LC

**Detector:** UV 254 nm

**Column:** 4.6-mm × 25-cm; packing L51

**Flow rate:** 0.75 mL/min

**Injection volume:** 5 μL

#### System suitability

**Sample:** *System suitability solution*

[NOTE—The relative retention times for brinzolamide and brinzolamide related compound A are 1.0 and 1.2, respectively.]

#### Suitability requirements

**Resolution:** NLT 1.8 between brinzolamide and brinzolamide related compound A peaks

**Column efficiency:** NLT 2000 theoretical plates for the brinzolamide peak

**Tailing factor:** NMT 1.8 for the brinzolamide peak

#### Analysis

**Sample:** *Sample solution*

Calculate the percentage of brinzolamide related compound A in the portion of Brinzolamide taken:

$$\text{Result} = (r_U/r_T) \times 100$$

$r_U$  = peak response for brinzolamide related compound A

$r_T$  = sum of the peak responses for brinzolamide and brinzolamide related compound A

**Acceptance criteria:** NMT 0.5%

#### ORGANIC IMPURITIES

**Buffer:** Prepare as directed in the *Assay*.

**Mobile phase A:** Prepare as directed for *Mobile phase* in the *Assay*.

**Mobile phase B:** Acetonitrile and *Buffer* (35:65)

**System suitability solution:** 0.1 mg/mL each of USP Brinzolamide RS and USP Brinzolamide Related Compound B RS in *Mobile phase A*

**Sample solution:** 1 mg/mL of Brinzolamide in *Mobile phase A*

#### Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

**Mode:** LC

**Detector:** UV 230 nm

**Column:** 4.6-mm × 25-cm; 5-μm packing L1

**Flow rate:** 1.0 mL/min

**Injection volume:** 10 μL

#### System suitability

**Sample:** *System suitability solution*

Use *Mobile phase A*.

[NOTE—The relative retention times for brinzolamide related compound B and brinzolamide are 0.8 and 1.0, respectively.]

#### Suitability requirements

**Resolution:** NLT 2.0 between the brinzolamide and brinzolamide related compound B peaks

**Column efficiency:** NLT 1200 theoretical plates for the brinzolamide peak

**Tailing factor:** NMT 2.0 for the brinzolamide peak

#### Analysis 1

Use *Mobile phase A*.

**Sample:** *Sample solution*

Allow the elution to continue for 20 min, and measure the areas for all the peaks, excluding the peaks of *Mobile phase A*.

Calculate the percentage of each impurity in the portion of Brinzolamide taken:

$$\text{Result} = (r_U/r_T) \times 100$$

$r_U$  = peak response for each impurity

$r_T$  = sum of all the peak responses

**Acceptance criteria 1:** NMT 0.3% for any individual impurity

**Analysis 2**

Use *Mobile phase B*.

**Sample:** *Sample solution*

Allow the elution to continue for 20 min, and measure the areas for brinzolamide and all the peaks having a relative retention greater than 6.

Calculate the percentage of each impurity in the portion of Brinzolamide taken:

$$\text{Result} = (r_U/r_T) \times 100$$

$r_U$  = peak response for each impurity

$r_T$  = sum of all the peak responses

**Acceptance criteria 2:** NMT 0.3% for any individual impurity; NMT 1.0% for total impurities from *Analysis 1* and *Analysis 2*

**SPECIFIC TESTS****• LOSS ON DRYING** (731)

**Analysis:** Dry under vacuum at 100°–105° for 3 h.

**Acceptance criteria:** NMT 0.5%

**ADDITIONAL REQUIREMENTS**

**• PACKAGING AND STORAGE:** Preserve in well-closed containers.

**• USP REFERENCE STANDARDS** (11)

USP Brinzolamide RS

USP Brinzolamide Related Compound A RS

Brinzolamide (*S*)-isomer.

$C_{12}H_{21}N_3O_5S_3$  383.52

USP Brinzolamide Related Compound B RS

(*R*-4-Amino)-2,3-dihydro-2-(3-methoxypropyl)-4*H*-thieno[3,2-*e*]-thiazine-6-sulfonamide-1,1-dioxide ethandiolate 1:1.

$C_{10}H_{17}N_3O_5S_3 \cdot C_2H_2O_4$  445.49

**Mobile phase:** Methanol and *Buffer* (35:65)

**Standard solution A:** 0.2 mg/mL of USP Brinzolamide RS in *Mobile phase*

**System suitability solution:** 0.06 mg/mL of USP Brinzolamide Related Compound B RS in *Standard solution A*

**Sample solution:** Nominally 0.2 mg/mL of brinzolamide in *Mobile phase* prepared as follows. Transfer a volume of Ophthalmic Suspension, equivalent to 10 mg of brinzolamide, into a 50-mL volumetric flask, and dilute with *Mobile phase* to volume.

**Chromatographic system**

(See *Chromatography* (621), *System Suitability*.)

**Mode:** LC

**Detector:** UV 254 nm

**Column:** 4.6-mm  $\times$  15-cm; 5- $\mu$ m packing L1

**Flow rate:** 1.0 mL/min

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

**System suitability**

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

[NOTE—The relative retention times for brinzolamide related compound B are between 0.48 and 0.61, and the relative retention time for brinzolamide is 1.0.]

**Suitability requirements**

**Resolution:** NLT 4.5 between the brinzolamide and brinzolamide related compound B peaks, *System suitability solution*

$\blacktriangle$  <sup>USP38</sup>

**Tailing factor:** NMT 2.0, *System suitability solution*

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

**Analysis**

**Samples:** *Standard solution A* and *Sample solution*

Calculate the percentage of the labeled amount of brinzolamide ( $C_{12}H_{21}N_3O_5S_3$ ) in the portion of Ophthalmic Suspension 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 *Standard solution A*

$C_S$  = concentration of USP Brinzolamide RS in *Standard solution A* (mg/mL)

$C_U$  = nominal concentration of brinzolamide in the *Sample solution* (mg/mL)

**Acceptance criteria:** 90.0%–110.0%

**IMPURITIES****Change to read:****• LIMIT OF BRINZOLAMIDE RELATED COMPOUND A**

**Mobile phase:** Dehydrated alcohol,  $\blacktriangle$ chromatographic hexane,  $\blacktriangle$  <sup>USP38</sup> methanol, and diethylamine (55: 40: 5: 0.2)

**System suitability solution:** 0.4 mg/mL of USP Brinzolamide RS and 0.02 mg/mL of USP Brinzolamide Related Compound A RS in dehydrated alcohol

**Sample solution:** Transfer a volume of Ophthalmic Suspension, equivalent to 10 mg of brinzolamide, to a 25-mL volumetric flask. Dilute with alcohol to volume.

**Chromatographic system**

(See *Chromatography* (621), *System Suitability*.)

**Mode:** LC

**Detector:** UV 254 nm

**Column:** 4.6-mm  $\times$  25-cm; packing L51

**Flow rate:** 0.75 mL/min

**Injection volume:** 5  $\mu$ L

**System suitability**

**Sample:** *System suitability solution*

[NOTE—The relative retention times for brinzolamide and brinzolamide related compound A are 1.0 and

**Brinzolamide Ophthalmic Suspension****DEFINITION**

Brinzolamide Ophthalmic Suspension is a sterile, aqueous suspension of Brinzolamide containing a suitable antimicrobial preservative. It contains NLT 90.0% and NMT 110.0% of the labeled amount of brinzolamide ( $C_{12}H_{21}N_3O_5S_3$ ).

**IDENTIFICATION**

**• A.** The retention time of the major peak of the *Sample solution* corresponds to that of *Standard solution A*, as obtained in the *Assay*.

**ASSAY****Change to read:****• PROCEDURE**

**Buffer:** 11.75 g/L of ammonium acetate in water. Adjust with acetic acid to a pH of 5.2.