

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 × 15-cm; 5- μ m packing L1

Flow rate: 1.0 mL/min

Injection volume: 20 μ 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*

▲^{USP38}

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, ▲^{USP38}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: 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 × 25-cm; packing L51

Flow rate: 0.75 mL/min

Injection volume: 5 μ 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.

Suitability requirements

Resolution: NLT 1.8 between the 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 Ophthalmic Suspension 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 1.5%

ORGANIC IMPURITIES

Buffer, Mobile phase, Standard solution A, System suitability solution, Sample solution, Chromatographic system, and System suitability: Proceed as directed in the *Assay*.

Standard solution B: 2.5 µg/mL of USP Brinzolamide Related Compound B RS in *Mobile phase*

Analysis

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

Calculate the percentage of each impurity in the portion of Ophthalmic Suspension taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response for each impurity from the *Sample solution*

r_S = peak response for brinzolamide related compound B from *Standard solution B*

C_S = concentration of USP Brinzolamide Related Compound B RS in *Standard solution B* (mg/mL)

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

M_{r1} = molecular weight of des-ethyl brinzolamide, 356.46

M_{r2} = molecular weight of des-ethyl brinzolamide oxalate, 445.49

Acceptance criteria

Any individual impurity: NMT 0.5%

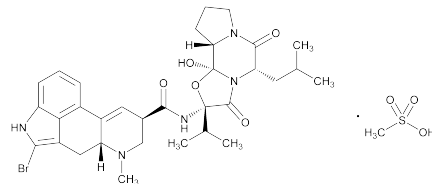
Total impurities: NMT 2.0%

SPECIFIC TESTS

- **STERILITY TESTS** (71): It meets the requirements when tested as directed for *Test for Sterility of the Product to be Examined, Membrane Filtration*.
- **pH** (791): 6.5–8.5

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers. Store at a temperature between 4° and 30°.
- **USP REFERENCE STANDARDS** (11)
 - USP Brinzolamide RS
 - USP Brinzolamide Related Compound A RS
Brinzolamide (*S*)-isomer.
C₁₂H₂₁N₃O₅S₃ 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 ethandioate 1:1.
C₁₀H₁₇N₃O₅S₃ · C₂H₂O₄ 445.49

Bromocriptine Mesylate

C₃₂H₄₀BrN₅O₅ · CH₄SO₃ 750.70
Ergotaman-3',6',18-trione, 2-bromo-12'-hydroxy-2'-(1-methylethyl)-5'-(2-methylpropyl)-, monomethanesulfonate (salt), (5 α)-; 2-Bromoergocryptine monomethanesulfonate (salt) [22260-51-1].

DEFINITION

Bromocriptine Mesylate contains NLT 98.0% and NMT 102.0% of C₃₂H₄₀BrN₅O₅ · CH₄SO₃, calculated on the dried basis.

IDENTIFICATION

- **A. INFRARED ABSORPTION** (197M): Undried
- **B. ULTRAVIOLET ABSORPTION** (197U)
Sample solution: 50 µg/mL in 0.1 M methanolic methanesulfonic acid
Acceptance criteria: Meets the requirements

ASSAY**PROCEDURE**

Sample solution: 600 mg of Bromocriptine Mesylate
Analysis: Dissolve with 80 mL of a mixture of acetic anhydride and glacial acetic acid (7:1). Titrate with 0.1 N perchloric acid VS. Perform a blank determination, and make any necessary correction (see *Titrimetry* (541)). Each mL of 0.1 N perchloric acid is equivalent to 75.07 mg of C₃₂H₄₀BrN₅O₅ · CH₄SO₃.
Acceptance criteria: 98.0%–102.0% on the dried basis

IMPURITIES**Inorganic Impurities**

- **RESIDUE ON IGNITION** (281): NMT 0.1%

Delete the following:

- **HEAVY METALS, Method II** (231): NMT 20 ppm (Official 1, Dec-2015)

Organic Impurities

- **PROCEDURE 1: LIMIT OF METHANESULFONIC ACID CONTENT**
Sample solution: 400 mg of Bromocriptine Mesylate
Analysis: Dissolve with 70 mL of methanol. Titrate under nitrogen with 0.1 N methanolic potassium hydroxide VS. Perform a blank determination, and make any necessary correction (see *Titrimetry* (541)). Each mL of 0.1 N methanolic potassium hydroxide is equivalent to 9.61 mg of CH₃SO₃H.
Acceptance criteria: NLT 12.5% and NMT 13.4% of CH₃SO₃H on the dried basis
- **PROCEDURE 2**
Solution A: 0.1 N citric acid solution. Adjust with hydrochloric acid to a pH of 2.0.
Diluent: Methanol and *Solution A* (1:1)
Solution B: Acetonitrile and 0.01 M phosphate buffer, pH 7.0 (2:3)
Solution C: Acetonitrile and 0.01 M phosphate buffer, pH 7.0 (3:2)
Mobile phase: See the gradient table below.