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 ethandioate 1:1.
  $C_{10}H_{17}N_3O_5S_3 \cdot C_2H_2O_4$ 445.49

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.
  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-µm packing L1
  Flow rate: 1.0 mL/min
  Injection volume: 20 µL
  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, ▲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 µL
  System suitability
  Sample: *System suitability solution*
  [NOTE—The relative retention times for brinzolamide and brinzolamide related compound A are 1.0 and

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

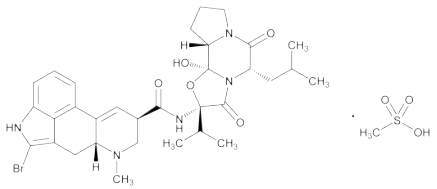
- **STERILITY TESTS ⟨71⟩:** It meets the requirements when tested as directed for *Test for Sterility of the Product to Be Examined, Membrane Filtration*.
- **pH ⟨791⟩:** 6.5–8.5

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.
$C_{12}H_{21}N_3O_5S_3$ 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 ethandioate 1:1.
$C_{10}H_{17}N_3O_5S_3 \cdot C_2H_2O_4$ 445.49

Bromocriptine Mesylate



$C_{32}H_{40}BrN_5O_5 \cdot CH_4SO_3$ 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 $C_{32}H_{40}BrN_5O_5 \cdot CH_4SO_3$, 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 $C_{32}H_{40}BrN_5O_5 \cdot CH_4SO_3$.
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 CH_3SO_3H.
Acceptance criteria: NLT 12.5% and NMT 13.4% of CH_3SO_3H 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.

USP Monographs