Ophthalmic Ointment Monographs: Tobramycin Ophthalmic Ointment

Type of Posting	Revision Bulletin
Posting Date	29–Jul–2016
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Expert Committee	Chemical Medicines Monographs 1 to 6
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015-2020 Council of Experts, the Chemical Medicines Expert Committees 1 to 6 has revised the monographs listed below. The purpose of the revision is to replace the requirement to comply with the entire content of the USP general chapter *Ophthalmic Products—Quality Tests* <771> with a requirement to comply only with the subsection for *Particulate and Foreign Matter* in *Ophthalmic Products—Quality Tests* <771>, and with the section for *Container Content* for those monographs where the requirement for Minimum Fill was deleted.

- Atropine Sulfate Ophthalmic Ointment
- Bacitracin Ophthalmic Ointment
- Bacitracin Zinc and Polymyxin B Sulfate Ophthalmic Ointment
- Bland Lubricating Ophthalmic Ointment
- Chloramphenicol and Polymyxin B Sulfate Ophthalmic Ointment
- Chloramphenicol Ophthalmic Ointment
- Chlortetracycline Hydrochloride Ophthalmic Ointment
- Ciprofloxacin Ophthalmic Ointment
- Dexamethasone Sodium Phosphate Ophthalmic Ointment
- Erythromycin Ophthalmic Ointment
- Gentamicin and Prednisolone Acetate Ophthalmic Ointment
- Gentamicin Sulfate Ophthalmic Ointment
- Hydrocortisone Acetate Ophthalmic Ointment
- Idoxuridine Ophthalmic Ointment
- Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Hydrocortisone Acetate Ophthalmic Ointment
- Neomycin and Polymyxin B Sulfates and Bacitracin Ophthalmic Ointment
- Neomycin and Polymyxin B Sulfates and Bacitracin Zinc Ophthalmic Ointment
- Neomycin and Polymyxin B Sulfates and Dexamethasone Ophthalmic Ointment
- Neomycin and Polymyxin B Sulfates Ophthalmic Ointment
- Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Hydrocortisone Ophthalmic Ointment
- Neomycin and Polymyxin B Sulfates, Bacitracin, and Hydrocortisone Acetate Ophthalmic Ointment
- Neomycin Sulfate and Dexamethasone Sodium Phosphate Ophthalmic Ointment
- Neomycin Sulfate Ophthalmic Ointment
- Oxytetracycline Hydrochloride and Polymyxin B Sulfate Ophthalmic Ointment
- Sodium Chloride Ophthalmic Ointment
- Sulfacetamide Sodium and Prednisolone Acetate Ophthalmic Ointment
- Sulfacetamide Sodium Ophthalmic Ointment
- Tetracycline Hydrochloride Ophthalmic Ointment
- Tobramycin and Dexamethasone Ophthalmic Ointment
- Tobramycin Ophthalmic Ointment

The Revision Bulletins for the monographs listed above supersede the currently official version of these monographs. The Revision Bulletin will be incorporated in the *First Supplement to USP 40–NF 35*.

Should you have any questions, please contact Margareth R. C. Marques, M.Sc., Ph.D. (301-816-8106 or mrm@usp.org).

Tobramycin Ophthalmic Ointment

DEFINITION

Tobramycin Ophthalmic Ointment contains NLT 90.0% and NMT 120.0% of the labeled amount of tobramycin ($C_{18}H_{37}N_5O_9$).

IDENTIFICATION

Change to read:

- **A. THIN-LAYER CHROMATOGRAPHY**

Diluent: Butyl alcohol and pyridine (100:1)

Standard solution: 6 mg/mL of USP Tobramycin RS in water

Sample solution: Vigorously shake by mechanical means a quantity of Ophthalmic Ointment, containing nominally 3 mg of tobramycin with 2 mL of chloroform. Add 1 mL of water, shake vigorously by mechanical means for 1 min, and centrifuge for 15 min. Use the clear upper, aqueous layer.

Solution A: *Standard solution* and *Sample solution* (1:1)

Chromatographic system

▲(See *Chromatography* ⟨621⟩*, Thin-Layer Chromatography*.)▲*USP39*

Adsorbent: 0.25-mm layer of chromatographic silica gel mixture

Application volume: 3 µL

Developing solvent system: Methanol, chloroform, and ammonium hydroxide (60:25:30)

Spray reagent: 10 mg/mL of ninhydrin in *Diluent*

Analysis

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

Apply the *Standard solution*, the *Sample solution*, and *Solution A* to the plate. Place the plate in a suitable chromatographic chamber, and develop the chromatogram in the *Developing solvent system* until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the chamber, allow the solvent to evaporate, and heat the plate at 110° for 15 min. Immediately locate the spots on the plate by spraying it with *Spray reagent*.

Acceptance criteria: Tobramycin appears as a pink spot, and the R_F values of the spots of the *Sample solution* and of *Solution A*, respectively, correspond to those of the *Standard solution*.

ASSAY

- **PROCEDURE**

Mobile phase: Dissolve 2.0 g of tris(hydroxymethyl)aminomethane in 800 mL of water. Add 20 mL of 1 N sulfuric acid, and dilute with acetonitrile to obtain 2000 mL of solution. Cool, and pass through a filter of 0.2-µm or finer pore size.

Solution A: 10 mg/mL of 2,4-dinitrofluorobenzene in alcohol. This solution may be used for 5 days if refrigerated when not in use.

Solution B: 15 mg/mL of tris(hydroxymethyl)aminomethane in water. This solution may be used for 1 month if refrigerated when not in use.

Solution C: 3 mg/mL of tris(hydroxymethyl)aminomethane prepared as follows. Transfer 40 mL of *Solution B* to a 200-mL volumetric flask. Add dimethyl sulfoxide while mixing, and dilute with dimethyl sulfoxide to volume. Use this reagent within 4 h. If kept immersed in an ice-water bath below 10°, the reagent may be used for up to 8 h.

Standard stock solution: 1.1 mg of USP Tobramycin RS prepared as follows. Transfer 55 mg of USP Tobramycin RS into a 50-mL volumetric flask. Add 1 mL of 1 N sulfuric acid and enough water to dissolve it, and dilute with water to volume.

Standard solution: 0.22 mg/mL of USP Tobramycin RS from *Standard stock solution* in water

Sample solution: Nominally 0.045 mg/mL of tobramycin from Ophthalmic Ointment in water prepared as follows. Transfer a portion of Ophthalmic Ointment, containing nominally 4.5 mg of tobramycin, to a separator. Add 50 mL of ether, and extract with four 20- to 25-mL portions of water. Combine the water extracts in a 100-mL volumetric flask, and dilute with water to volume.

Derivatized standard solution, Derivatized sample solution, and Blank solution: Proceed as follows. Heat all solutions at the same temperature and for the same duration of time as indicated. Move all flasks to and from the 60° constant temperature bath at the same time.

To separate 50-mL volumetric flasks transfer 4.0 mL of the *Standard solution*, 15.0 mL of the *Sample solution*, and 4.0 mL of water. To each flask add 10 mL of *Solution A* and 10 mL of *Solution C*, shake, and insert the stopper. Place the flasks in a constant temperature bath at 60 ± 2°, and heat for 50 ± 5 min. Remove the flasks from the bath, and allow to stand for 10 min. Add acetonitrile to about 2 mL below the 50-mL mark, allow to cool to room temperature, then dilute with acetonitrile to volume. The solutions thus obtained are the *Derivatized standard solution*, the *Derivatized sample solution*, and the *Blank solution*, respectively.

System suitability stock solution: 0.24 mg/mL of *p*-naphtholbenzein in acetonitrile. Prepare freshly.

System suitability solution: Transfer 2 mL of the *System suitability stock solution* to a 10-mL volumetric flask, dilute with *Derivatized standard solution* to volume, and use promptly.

Chromatographic system

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

Mode: LC

Detector: UV 365 nm

Column: 3.9-mm × 30-cm; packing L1

Flow rate: 1.2 mL/min

Injection volume: 20 µL

System suitability

Samples: *Derivatized standard solution* and *System suitability solution*

[NOTE—The relative retention times for *p*-naphtholbenzein and tobramycin are about 0.6 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 4.0 between *p*-naphtholbenzein and tobramycin, *System suitability solution*

Relative standard deviation: NMT 2.0%, *Derivatized standard solution*

Analysis

Samples: *Derivatized standard solution*, *Derivatized sample solution*, and *Blank solution*

Use the *Blank solution* to identify the solvent and reagent peaks.

Calculate the percentage of the labeled amount of tobramycin ($C_{18}H_{37}N_5O_9$) in the portion of Ophthalmic Ointment taken:

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

r_U = peak area of tobramycin from the *Derivatized sample solution*

r_S = peak area of tobramycin from the *Derivatized standard solution*

C_S = concentration of USP Tobramycin RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of tobramycin in the *Sample solution* (mg/mL)
P = potency of tobramycin in USP Tobramycin RS (µg/mg)
F = conversion factor, 0.001 mg/µg
Acceptance criteria: 90.0%–120.0%

PERFORMANCE TESTS

Delete the following:

▲• **MINIMUM FILL** ⟨**755**⟩**:** Meets the requirements
▲*USP39*

SPECIFIC TESTS

Change to read:

• **STERILITY TESTS** ⟨**71**⟩**:** ▲ Meets the requirements
▲*USP39*

Delete the following:

▲• **WATER DETERMINATION,** *Method I* ⟨**921**⟩
Analysis: Use 20 mL of a mixture of toluene and methanol (7:3) in place of methanol in the titration vessel.
Acceptance criteria: NMT 1.0%
▲*USP39*

Delete the following:

▲• **METAL PARTICLES IN OPHTHALMIC OINTMENTS** ⟨**751**⟩**:** Meets the requirements
▲*USP39*

Change to read:

▲• **OTHER REQUIREMENTS:** It meets the requirements •for *Particulate and Foreign Matter* and *Container Contents*.• (RB 1-Aug-2016) in *Ophthalmic Products—Quality Tests* ⟨771⟩, •*Drug Product Quality, Universal Tests, Particulate and Foreign Matter* and *Container Contents*.• (RB 1-Aug-2016)
▲*USP39*

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in collapsible ophthalmic ointment tubes.
• **USP REFERENCE STANDARDS** ⟨**11**⟩
USP Tobramycin RS