Ophthalmic Ointment Monographs: Erythromycin 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).

Erythromycin Ophthalmic Ointment

DEFINITION

Erythromycin Ophthalmic Ointment is a sterile preparation of Erythromycin in a suitable ointment base. It contains NLT 90.0% and NMT 120.0% of the labeled amount of erythromycin ($C_{37}H_{67}NO_{13}$).

IDENTIFICATION

• **A. THIN-LAYER CHROMATOGRAPHY**

Standard solution: 2.5 mg/mL of USP Erythromycin RS in methanol

Sample solution: 2.5 mg/mL of erythromycin from Ophthalmic Ointment in methanol prepared as follows. Transfer an amount of Ophthalmic Ointment containing nominally 5 mg of erythromycin to a separator containing 50 mL of solvent hexane. Shake until dissolved. Extract with three separate 20-mL portions of methanol. Combine the methanol extracts in a beaker, and evaporate to dryness. Dissolve the residue in 2 mL of methanol.

Chromatographic system

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

Adsorbent: 0.25-mm layer of chromatographic silica gel

Application volume: 10 µL

Developing solvent system: Methanol and chloroform (85:15)

Spray reagent: Alcohol, *p*-methoxybenzaldehyde, and sulfuric acid (90:5:5)

Analysis

Samples: *Standard solution* and *Sample solution*

Apply the *Standard solution* and the *Sample solution* to the plate. Place the plate in an unlined chromatographic chamber, and develop the chromatogram using the *Developing solvent system* until the solvent front has moved about 7 cm. Remove the plate from the chamber, mark the solvent front, and allow the solvent to evaporate. Spray the plate with *Spray reagent*. Heat the plate at 100° for 10 min, and examine the chromatogram, in which erythromycin appears as a black-to-purple spot.

Acceptance criteria: The R_F value of the principal spot of the *Sample solution* corresponds to that of the *Standard solution*.

ASSAY

Change to read:

• **PROCEDURE**

Solution A: Acetonitrile and water (90:10). Store in a reservoir protected from air by sparging with helium.

▲Solution B: 0.04 mg/mL of sodium hydroxide in water ▲*USP39*

Mobile phase: ▲*Solution A* and *Solution B* (56:44)▲*USP39*

Diluent: Methanol and water (50:50)

Standard solution 1: 0.66 mg/mL of USP Erythromycin RS in *Diluent*

Standard solution 2: 0.034 mg/mL of USP Erythromycin B RS and USP Erythromycin C RS in *Diluent*

System suitability solution: Transfer 2 mg of USP Erythromycin Related Compound N RS to a 10-mL volumetric flask, add 0.4 mL of *Standard solution 1* and 6 mL of *Standard solution 2*, and mix. Dilute with *Standard solution 2* to volume.

Sample solution: Nominally 0.6 mg/mL of erythromycin from Ophthalmic Ointment in *Diluent* prepared as follows. Transfer an amount of Ophthalmic Ointment containing nominally 60 mg of erythromycin to a 125-mL separator. Add 50 mL of solvent hexane, and shake until dissolved. Extract with four separate 20-mL portions of *Diluent*, collecting the extracts in a 100-mL volumetric flask. Dilute the combined extracts with *Diluent* to volume, and pass a portion of the solution through ▲a suitable filter.▲*USP39* Use the clear filtrate.

Chromatographic system

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

Mode: LC

Detector: Pulsed amperometric electrochemical detector ▲▲*USP39*

Electrode: Glassy carbon ▲▲*USP39*

Waveform: See *Table 1*.

Table 1

Time (s)	Potential (V)	Integration
0.00	+0.9	—
0.40	+0.9	Begin
0.50	+0.9	End
0.60	-0.9	—

Columns

Guard: 4-mm × 5-cm; 8-µm packing L50

Analytical: 4-mm × 25-cm; 8-µm packing L50

Flow rate: 1 mL/min

Injection volume: 10 µL

System suitability

Samples: *Standard solution 1* and *System suitability solution*

[NOTE—For relative retention times, see *Table 2*.]

Table 2

Peak	Relative Retention Time
Erythromycin related compound N	0.4
Erythromycin C	0.5
Erythromycin A	1.0
Erythromycin B	1.6

Suitability requirements

Resolution: NLT 0.6 between erythromycin related compound N and erythromycin C; NLT 2.5 between erythromycin C and erythromycin A; NLT 2.5 between erythromycin A and erythromycin B, *System suitability solution*

Tailing factor: NMT 2, *Standard solution 1*

Relative standard deviation: NMT 3%, *Standard solution 1*

Analysis

Samples: *Standard solution 1*, *Standard solution 2*, and *Sample solution*

Calculate the percentage of erythromycin A relative to the labeled amount of erythromycin 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 erythromycin A from the *Sample solution*

r_S = peak area of erythromycin A from *Standard solution 1*

C_S = concentration of USP Erythromycin RS in *Standard solution 1* (mg/mL)

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

P = potency of erythromycin A in USP Erythromycin RS (µg/mg)
F = conversion factor, 0.001 mg/µg

Calculate the percentage of erythromycin B relative to the labeled amount of erythromycin in the portion of Ophthalmic Ointment taken:

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

r_U = peak area of erythromycin B from the *Sample solution*
r_S = peak area of erythromycin B from *Standard solution 2*
C_S = concentration of USP Erythromycin B RS in *Standard solution 2* (mg/mL)
C_U = nominal concentration of erythromycin in the *Sample solution* (mg/mL)
P = potency of erythromycin B in USP Erythromycin B RS (mg/mg)

Calculate the percentage of erythromycin C relative to the labeled amount of erythromycin in the portion of Ophthalmic Ointment taken:

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

r_U = peak area of erythromycin C from the *Sample solution*
r_S = peak area of erythromycin C from *Standard solution 2*
C_S = concentration of USP Erythromycin C RS in *Standard solution 2* (mg/mL)
C_U = nominal concentration of erythromycin in the *Sample solution* (mg/mL)
P = potency of erythromycin C in USP Erythromycin B RS (mg/mg)

Calculate the percentage of the labeled amount of erythromycin in the Ophthalmic Ointment by adding the percentages of erythromycin A, erythromycin B, and erythromycin C.

Acceptance criteria: 90.0%–120.0%

PERFORMANCE TESTS

Delete the following:

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

SPECIFIC TESTS

• **STERILITY TESTS** ⟨**71**⟩**:** It meets the requirements.

Delete the following:

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

Delete the following:

▲• **WATER DETERMINATION** ⟨**921**⟩**,** *Method I*
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*

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

Change to read:

• **PACKAGING AND STORAGE:** Preserve in collapsible ophthalmic ointment tubes. ▲Store at controlled room temperature.▲*USP39*

Change to read:

• **USP REFERENCE STANDARDS** ⟨**11**⟩
USP Erythromycin RS
▲USP Erythromycin B RS
USP Erythromycin C RS
USP Erythromycin Related Compound N RS▲*USP39*