USP 28

Hydroxyamphetamine H

um molybdate in 10 mL of out 2 mg of Hydroxyamblue color is produced nds such as amphetamine phenolic hydroxyl, do not

water, and add a solution of water. Extract with two 10er solution to evaporate to yamphetamine so obtained I under Melting Range or

n 10 mL of water add 1 mL S: a pale yellow precipitate ammonium hydroxide. 1 192°

2 hours: it loses not more

an 0.1%.

ut 400 mg, and dissolve in ind 10 mL of glacial acetic th 0.1 N silver nitrate VS. ent to 7.990 mg of Br. the sis, is between 33.6% and

thanol, and ammonium

cyamphetamine Hydrobro 0 mL of glacial acetic acid 1g slightly, if necessary, to itrate with 0.1 N perchloric and make any necessary icid is equivalent to 23.21

# /drobromide

promide Ophthalmic aqueous solution of ide. It contains not than 105.0 percent of ·HBr. It contains a

, light-resistant containers. Hydroxyamphetamine Hy-

im molybdate in 10 mL of c Solution: an intense blue amino compounds such as hich, lacking a phenolic

nine obtained in the Assay under Melting Range or en beginning and end of

D under Hydroxyamphet-

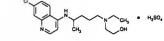
lution, equivalent to about mide, with 0.01 N hydro-

moric acid to 25 mL, and proceed as directed under Identification-Organic Nitrogenous Bases (181), using sodium carbonate TS in place of 1 N sodium hydroxide, beginning with "Transfer the liquid to a separator": the Ophthalmic Solution meets the requirements of the test.

sterility (71): meets the requirements. pH (791): between 4.2 and 6.0.

Assay—Transfer an accurately measured volume of Ophthalmic Solution, equivalent to about 100 mg of hydroxyamphetamine bydrobromide, to a 125-mL separator. Wash the solution with 15 mL of chloroform, and discard the washing. Rinse the stopper and the mouth of the separator with a few drops of water. Add 1.05 g of sodium bicarbonate, preventing it from coming in contact with the mouth of the separator, and swirl until most of the bicarbonate has dissolved. By means of a 1-mL syringe, rapidly inject 0.5 mL of acetic anhydride directly into the contents of the separator. acctic anny access an except into the separator, and shake vigorously until the evolution of carbon dioxide has ceased (7 to 10 minutes), releasing the pressure as necessary through the stopcock. Allow to stand for 5 minutes, and extract the solution with five 10-mL portions of chloroform, filtering each extract through a pledget of cotton, of chorotorin, intering each extract inforgin a pledger of cotton, previously washed with chloroform, into a tared 100-mL beaker. Evaporate the combined chloroform extracts on a steam bath in a current of air or stream of nitrogen to dryness. Dry the residue at  $80^{\circ}$ for 90 minutes, cool in a desiccator, and weigh. The weight of the diacetylhydroxyamphetamine so obtained, multiplied by 0.9866, represents the weight of  $C_9H_{13}NO$  HBr in the volume of Ophthalmic Solution taken.

## Hydroxychloroquine Sulfate



H26CIN3O · H2SO4 433.95

(±)-2-[[4-[(7-Chloro-4-quinolinyl)amino]pentyl]ethyl]amino-,
(±)-sulfate (1:1) (salt).
(±)-2-[[4-[(7-Chloro-4-quinolyl)amino]pentyl]ethylamino]ethanol sulfate (1:1) (salt) [747-36-4].

» Hydroxychloroquine Sulfate contains not less than 98.0 percent and not more than 102.0 percent of  $C_{18}H_{26}CIN_3O \cdot H_2SO_4$ , calculated on the dried basis.

Packaging and storage-Preserve in well-closed, light-resistant containers

USP Reference standards (11)-USP Hydroxychloroquine Sulfate RS

Identification-

A: Ultraviolet Absorption (197U)-

Solution: 10 µg per mL. Medium: dilute hydrochloric acid (1 in 100).

Loss on drying (731)—Dry it at 105° for 2 hours: it loses not more than 2.0% of its weight.

Ordinary impurities (466)— Test solution: 10% water in methanol. Standard solution: 10% water in methanol. Eluant: a mixture of alcohol, water, and ammonium hydroxide (80:16:4).

Visualization: 1.

Organic volatile impurities, Method I (467): meets the requirements.

Assay-Dissolve about 100 mg of Hydroxychloroquine Sulfate, accurately weighed, in about 5 mL of water, and dilute quantitatively and accurately be about 5 mL of water, and dilute accurately to obtain a and stepwise with dilute hydrochloric acid (1 in 100) to obtain a

solution containing about 10 µg per mL. Similarly prepare a Standard solution of USP Hydroxychloroquine Sulfate RS. Concomitantly determine the absorbances of both solutions in 1-cm cells at the wavelength of maximum absorbance at about 343 nm, with a suitable spectrophotometer, using dilute hydrochloric acid (1 in 100) as the blank. Calculate the quantity, in mg, of  $C_{18}H_{28}CIN_3O \cdot H_2SO_4$  in the portion of Hydroxychloroquine Sulfate taken by the formula:

#### $10C(A_U/A_s)$

in which C is the concentration, in  $\mu g$  per mL, of USP Hydroxychloroquine Sulfate RS in the Standard solution, and  $A_u$ and As are the absorbances of the solution of Hydroxychloroquine Sulfate and the Standard solution, respectively.

# Hydroxychloroquine Sulfate Tablets

» Hydroxychloroquine Sulfate Tablets contain not less than 93.0 percent and not more than 107.0 percent of the labeled amount of hydroxychloroquine sulfate  $(C_{18}H_{26}CIN_{3}O \cdot H_{2}SO_{4}).$ 

Packaging and storage-Preserve in tight, light-resistant containers. USP Reference standards (11)-USP Hydroxychloroquine Sulfate RS.

#### Identification-

A: Triturate a quantity of finely powdered Tablets, equivalent to about 1 g of hydroxychloroquine sulfate, with 50 mL of water, and filter: the clear filtrate so obtained meets the requirements for *Identification* tests *B* and *C*.

B: It meets the requirements under Identification-Organic Nitrogenous Bases (181)

C: A solution (1 in 100) meets the requirements of the tests for Sulfate  $\langle 191 \rangle$ .

**D**: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

Dissolution (711)-

water; 900 mL. Medium: Apparatus 2: 50 rpm.

Time: 60 minutes.

*Procedure*—Determine the amount of  $C_{18}H_{26}ClN_3O \cdot H_2SO_4$  dis-solved from UV absorbances at the wavelength of maximum absorbance at about 343 nm of filtered portions of the solution under test, suitably diluted with Dissolution Medium, if necessary, in comparison with a Standard solution having a known concentration

of USP Hydroxychloroquine Sulfate RS in the same medium. *Tolerances*—Not less than 70% (Q) of the labeled amount of  $C_{18}H_{26}CIN_3O \cdot H_2SO_4$  is dissolved in 60 minutes.

Uniformity of dosage units (905): meet the requirements.

Assay

Mobile phase-To 800 mL of water, add 100 mL of methanol, 100 mL of acetonitrile, 2.0 mL of phosphoric acid, and 96 mg of sodium l-pentanesulfonate, mix, and filter. Make adjustments if necessary

(see System Suitability under Chromatography (621)). Solvent mixture—Prepare a mixture of methanol and water (1:1). Standard preparation—Dissolve an accurately weighed quantity of USP Hydroxychloroquine Sulfate RS in Solvent mixture, dilute quantitatively with Solvent mixture, and mix to obtain Solution A having a known concentration of about 1 mg per mL. Transfer 5.0 mL of this solution to a 100-mL volumetric flask, dilute with *Mobile* phase to volume, and mix to obtain the *Standard preparation* having a known concentration of about 0.05 mg per mL

a known concentration of about 0.05 mg per mL. Resolution solution—Prepare a solution of chloroquine phosphate in methanol having a concentration of 1 mg per mL. Transfer 5.0 mL of this solution to a 100-mL volumetric flask, add 5.0 mL of Solution A, dilute with Mobile phase to volume, and mix. Assay preparation—Weigh and finely powder not less than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 200 mg of hydroxychloroquine sulfate to a 200-mL volumetric flask, add about 150 mL of Solvent mixture, and mix. Sonicate with intermitten thaking for about 15 minutes. and cool to Sonicate, with intermittent shaking, for about 15 minutes, and cool to

Heavy metals, Method II (231): 0.001%, 1 mL of hydroxylamine hydrochloride solution (1 in 5) being added to the solution of the residue.

Organic volatile impurities, Method IV (467): meets the requirements

Assay—[Caution—Hydriodic acid and its reaction byproducts are highly toxic. Perform all steps of the Assay preparation and the Standard preparation in a properly functioning hood. Specific safety practices to be followed are to be identified to the analyst performing this test.

Hydriodic acid—Use a reagent having a specific gravity of at least 1.69, equivalent to 55% HI.

Internal standard solution-Transfer about 2.5g of toluene accurately weighed, to a 100-mL volumetric flask containing 10 mL of o-xylene, dilute with o-xylene to volume, and mix.

Standard preparation—Into a suitable serum vial weigh about 135 mg of adipic acid and 4.0 mL of *Hydriodic acid*, pipet 4 mL of *Internal standard solution* into the vial, and close the vial securely with a suitable septum stopper. Weigh the vial and contents accurately, add 30 µL of isopropyl iodide through the septum with

accurately, add 30 µL of isopropyl iodide through the septum with a syringe, again weigh, and calculate the weight of isopropyl iodide added, by difference. Add 90 µL of methyl iodide similarly, again weigh, and calculate the weight of methyl iodide similarly, again weigh, and calculate the weight of methyl iodide added, by difference. Shake, and allow the layers to separate. *Assay preparation*—Transfer about 0.065 g of dried Hypromellose, accurately weighed, to a 5-mL thick-walled reaction vial equipped with a pressure-tight septum-type closure, add an amount of adipic acid equal to the weight of the test specimen, and pipet 2 mL of *Internal standard* into the vial. Cautiously pipet 2 mL of *Hydriodic* accurately. Mix the contents of the vial continuously, while heating at 150° for 60 minutes. Allow the vial to cool for about 45 minutes, and again weigh. If the weight loss is greater than 10 mg. discard the again weigh. If the weight loss is greater than 10 mg, discard the

again weigh. In the weight loss is greater than to hig, discate the mixture, and prepare another Assay preparation. Chromatographic system (see Chromatography (621))—The gas chromatograph is equipped with a thermal conductivity detector and a 4-mm  $\times$  1.8-m glass column packed with 20% liquid phase G28 on 100- to 120-mesh support S1C that is not silanized. Helium is used as the carrier gas and the temperature of the column is maintained at 130°. Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure*: the relative retention times are about 1.0, 2.2, 3.6, and 8.0 for methyl iodide, isopropyl iodide,

toluene, and o-xylene, respectively; and the resolution, R, between toluene and isopropyl iodide is not less than 2.0. *Calibration*—Inject about 2  $\mu$ L of the upper layer of the *Standard* preparation into the gas chromatograph, and record the chromatogram. Calculate the relative response factor,  $F_M$ , of equal weights of toluene and methyl iodide taken by the formula:

#### $Q_M/R_{SM}$

in which  $Q_M$  is the quantity ratio of methyl iodide to toluene in the Standard preparation, and R<sub>SM</sub> is the peak area ratio of methyl iodide to toluene obtained from the *Standard preparation*. Similarly, calculate the relative response factor,  $F_{i,j}$  of equal weights of toluene and isopropyl iodide taken by the formula:

#### $Q_I/R_{st}$

in which  $Q_i$  is the quantity ratio of isopropyl iodide to toluene in the Standard preparation, and  $R_{si}$  is the peak area ratio of isopropyl iodide to toluene obtained from the Standard preparation. Procedure—Inject about 2  $\mu$ L of the upper layer of the Assay preparation into the gas chromatograph, and record the chromatogram. Calculate the percentage of methoxy (-OCH<sub>3</sub>) in the Hypromellose taken by the formula:

#### $2(31/142)F_{M}R_{UM}(W_{T}/W_{U}),$

in which 31/142 is the ratio of the formula weights of methoxy and methyl iodide;  $F_M$  is defined under *Calibration*;  $R_{UM}$  is the ratio of the area of the methyl iodide peak to that of the toluene peak obtained from the Assay preparation;  $W_T$  is the weight, in g, of toluene in the Internal standard solution; and  $W_U$  is the weight, in g, of Hypromellose taken for the Assay. Similarly, calculate the percentage USP 28

of hydroxypropoxy (-OCH2CHOHCH3) in the Hypromellose takes by the formula:

2(

$$75/170)F_{I}R_{UI}(W_{T}/W_{U}),$$

in which 75/170 is the ratio of the formula weights of hydro xypropoxy and isopropyl iodide;  $F_i$  is defined under *Calibration*;  $F_i$ is the ratio of the area of the isopropyl iodide peak to that of the toluene peak obtained from the *Assay preparation*;  $W_r$  is the weight in g, of toluene in the *Internal standard solution*; and  $W_v$  is the weight, in g, of Hypromellose taken for the *Assay*.

# **Hypromellose Ophthalmic Solution**

» Hypromellose Ophthalmic Solution is a sterile solution of Hypromellose. It contains not less than 85.0 percent and not more than 115.0 percent of the labeled amount Hypromellose (hydroxypropyl methylcellulose). It ma contain suitable antimicrobial, buffering, and stabilizing agents.

#### Packaging and storage-Preserve in tight containers. USP Reference standards (11)---USP Hydroxypropyl Methylcell lose RS

Identification

A: It meets the requirements of Identification test C un Hypromellose.

B: Heat 5 mL of Ophthalmic Solution in a test tube over a flame: the warm solution turns cloudy but clears upon chilling. Sterility (71): meets the requirements.

pH (791): between 6.0 and 7.8.

Assay— Standard preparation—Dissolve a suitable quantity of U Hydroxypropyl Methylcellulose RS, accurately weighed, in wa and dilute quantitatively with water to obtain a solution having known concentration of about 100 µg per mL.

Assay preparation—Dilute an accurately measured volume Ophthalmic Solution quantitatively with water to obtain a solution having an equivalent concentration of about 100 µg of hypromella per mL

Procedure-Pipet 2 mL each of the Standard preparation, Assay preparation, and water to provide a blank, into separate, glas stoppered test tubes. To each tube add 5.0 mL of diphenyland solution (prepared by dissolving 3.75 g of colorless diphenylam crystals in 150 mL of glacial acetic acid and diluting the solution w 90 mL of hydrochloric acid) mix and installing the solution w 90 mL of hydrochloric acid), mix, and immediately insert the minto an oil bath at  $105^{\circ}$  to  $110^{\circ}$  for 30 minutes, the temperature betweet uniform within  $0.1^{\circ}$  during heating. Remove the tubes, and plather in an ice-water bath for 10 minutes or until thoroughly cool. room temperature and using a suitable spectrophotometer, conc itantly determine the absorbances of the solutions from the Stand preparation and the Assay preparation at 635 nm, using the way solution as the blank. Calculate the quantity, in mg, of hypromello in each mL of the Ophthalmic Solution taken by the formula:

### $0.001C(d/V)(A_U/A_s),$

in which C is the concentration, in  $\mu$ g per mL, of USP Hydroxyp Methylcellulose RS in the *Standard preparation*; V is the volume mL, of Ophthalmic Solution taken; d is the dilution fold of V use obtain the Assay preparation; and  $A_U$  and  $A_s$  are the absorbances the solutions from the Assay preparation and the Stat preparation, respectively.

SP 28

# buprofen

EH18O2 206.28 neacetic acid, a-n 

H) Mixture [58560

Ibuprofen contair nore than 103.0 pe hydrous basis.

#### ickaging and storage SP Reference standa ntification-

A: Infrared Absorptic B: Ultraviolet Abso Solution: 250 μg pe Medium: 0.1 N sodi Respective absorptivi rous basis, do not C: The chromatogr nected in the Assay presponds to that exh. aration, obtained as ater, Method I (921): isidue on ignition (28 wy metals, Method nomatographic puri Mobile phase—Prepa viously adjusted wi tonitrile (1340:680). Wability under Chrom. Det proparation. Test preparation-Pre taining about 5 mg p Resolution solutioneach mL about 5 mg Chromatographic sy. × 15-cm column ained at  $30 \pm 0.2^{\circ}$ atomatograph a series dition the column. C ford the peak response intion times are about the resolution, R, profen peak is not les profen peak is not les procedure—[NOTE—U dicated.] Inject about ponatograph, record ponses. Calculate the mula:

which  $r_i$  is the respc went peak and the ma ponses of all the peal the individual impurit anic volatile imp rements

nt-Use dimethy of 4-isobutylaceto preparation and th

Slayback Exhibit 1055, Page 41 of 78 Slayback v. Eye Therapies - IPR2022-00142

loride taken to prepare ation and the Stand

# : for Injection

Injection is a steri ride and Lactose. nt and not more th it of C26H27NO9 · HQ be taken to preve Hydrochloride d

#### tainers for Sterile Solid

Endotoxin RS. USP Ide

, it meets the requirem 5 (1).

he Assay preparation for idarubicin, the reter the chromatogram of ay.

; not more than 8.9 U ydrochloride, a solution 1 containing 0.07 mg sed in the Test Procedua when tested as directed rility of the Product to

ution constituted as dire liluent.

4.0%, the Test Prepara opic specimen. irements for Uniformity ider Injections (1).

tration, Resolution sol 1 as directed in the As

ntents of 1 container quantitatively with Dia out 0.5 mg of idaruby

Procedure under Idam n mg, of C<sub>26</sub>H<sub>27</sub>NO<sub>9</sub> HC le for Injection taken by

#### $v_{u}/r_{s}),$

µg per mL, of idaruli Standard preparation; bicin hydrochloride ini mg per mL, of idarubi 10 on the basis of the labe of dilution; and  $r_{U}$  and  $r_{s}$ ; obtained from the As ion, respectively.

f., IN<sub>2</sub>O; 354.10 tine, 2'-deoxy-5-iodo-. Deoxy-5-iodouridine [54-42-2].

doxuridine contains not less than 98.0 percent and not re than 101.0 percent of C<sub>9</sub>H<sub>11</sub>IN<sub>2</sub>O<sub>5</sub>, calculated on dried basis.

reging and storage-Preserve in tight, light-resistant containers. Reference standards (11)-USP Idoxuridine RS.

tification

Infrared Absorption (197M). Ultraviolet Absorption (197U)-

Solution:

aduiton: 35 µg per mL. Medium: pH 12.0 buffer (prepared from 7.46 g of potassium inde and 24 mL of 1 N sodium hydroxide dissolved in 2000 mL of

the only do not differ by more than 2.0%.

**For drying** (731)—Dry about 500 mg, accurately weighed, in time at 60° for 2 hours: it loses not more than 1.0% of its weight. -Dissolve about 250 mg of Idoxuridine, accurately weighed, m — Dissolve about 250 mg of Idoxuridine, accurately weighed, mL of dimethylformamide that previously has been neutralized 0.1 N sodium methoxide in toluene VS, a solution of 300 mg of a bill blue in 100 mL of methanol being used as the indicator. mol blue in 100 mL of methanol being used as the indicator. the with 0.1 N sodium methoxide in toluene VS to a blue point, taking precautions against absorption of atmospheric on dioxide. Perform a blank determination, and make any same correction. Each mL of 0.1 N sodium methoxide is ivalent to 35.41 mg of C<sub>9</sub>H<sub>11</sub>IN<sub>2</sub>O<sub>5</sub>.

# **Doxuridine Ophthalmic Ointment**

toxuridine Ophthalmic Ointment is Idoxuridine in a rolatum base. It contains not less than 0.45 percent not more than 0.55 percent of  $C_9H_{11}IN_2O_5$ . It is nie.

ubes in a cool place. Reference standards (11)—USP Idoxuridine RS.

tification-The UV absorption spectrum of the solution from the malmic Ointment employed for measurement of absorbance in Assay exhibits maxima and minima at the same wavelengths as of the Standard preparation prepared for the Assay. (ity (71): meets the requirements.

al particles—It meets the requirements of the test for Metal sciences in Ophthalmic Ointments (751).

the is fluffy. Transfer to a  $19 - \times 250$ -mm chromatographic tube Chromatography (621)) that contains a pledget of glass wool fitted with a stopcock at the bottom. Tamp gently to compress

promatographic column—Mix 4 g of chromatographic siliceous with 4 mL of 0.1 N hydrochloric acid in a glass mortar until the

niform mass.

Official Monographs / Idoxuridine 997

Standard preparation-Transfer about 25 mg of USP Idoxuridine RS, accurately weighed, to a 50-mL volumetric flask, add methanol to volume, and mix. Dilute 5.0 mL of this solution with a mixture of 1 volume of butyl alcohol and 5 volumes of chloroform to 100.0 mL, and mix

Assay preparation—Mix 4 g of chromatographic siliceous earth with 2 mL of 0.1 N hydrochloric acid in a glass mortar until the mixture is fluffy. Add a quantity of Ophthalmic Ointment, equivalent to about 5 mg of idoxuridine and accurately weighed, to the mixture, and mix.

Procedure—Transfer the Assay preparation to the prepared Chromatographic column. Transfer 2 g of chromatographic siliceous earth and 2 mL of 0.1 N hydrochloric acid to the glass mortar, and mix until fluffy, using this material to rinse the mortar and pick up any remaining Ophthalmic Ointment. Transfer about half of this mixture to the tube, and tamp gently until the column appears uniform. Transfer the remaining portion to the Chromatographic column, and tamp as before. Wipe the walls of the mortar with a small pledget of glass wool, and insert the pledget in the top of the column. Pass 50 mL of chloroform through the column at a flow rate of approximately 1 mL per minute, and discard the chloroform. Elute with about 200 This per limitate, and diseare the controlotion. Ende with about 200 mL of a mixture of 1 volume of butyl alcohol and 5 volumes of chloroform at the same flow rate, discarding the first 20 mL of the eluate. Collect the remainder of the eluate in a 200-mL volumetric flask, dilute with the eluting solvent to volume, and mix. Concomitantly determine the absorbances of this solution and the Standard preparation in 1-cm cells at 320 nm and at the wavelength of maximum absorbance at about 283 nm, with a suitable spectrophotometer, using a mixture of butyl alcohol and chloroform as the blank. Calculate the quantity, in mg, of C9H11IN2O5 in the Ophthalmic Ointment taken by the formula:

#### $0.2C(A_{283} - A_{320})_U/(A_{283} - A_{320})_s,$

in which C is the concentration, in  $\mu$ g per mL, of USP Idoxuridine RS in the *Standard preparation*; and the parenthetic expressions are the differences in the absorbances of the two solutions at the wavelengths indicated by the subscripts, for the solution from the Ophthalmic Ointment (U) and the Standard preparation (S), respectively.

# **Idoxuridine Ophthalmic Solution**

» Idoxuridine Ophthalmic Solution is a sterile, aqueous solution of Idoxuridine. It contains not less than 0.09 percent and not more than 0.11 percent of  $C_9H_{11}IN_2O_5$ . It may contain suitable buffers, stabilizers, and antimicrobial agents.

Packaging and storage-Preserve in tight, light-resistant containers in a cold place.

USP Reference standards (11)-USP Idoxuridine RS.

Identification-The UV absorption spectrum of the solution employed for measurement of absorbance in the Assay exhibits maxima and minima at the same wavelengths as that of the Standard preparation prepared for the Assay.

Sterility(71): meets the requirements.

pH (791): between 4.5 and 7.0.

Assay-

Chromatographic column and Standard preparation-Prepare as

directed in the Assay under Idoxuridine Ophthalmic Ointment. Assay preparation—Mix an accurately measured volume of Ophthalmic Solution, equivalent to about 5 mg of idoxuridine, with 3 g of chromatographic siliceous earth in a glass mortar until the mixture is fluffy.

oxuridine

Procedure-Proceed as directed for Procedure in the Assay under Idoxuridine Ophhalmic Ointment, omitting the treatment of the column with 50 mL of chloroform. Calculate the quantity, in mg, of C<sub>9</sub>H<sub>11</sub>IN<sub>2</sub>O<sub>5</sub> in each mL of the Ophthalmic Solution taken by the formula:

$$0.2C(A_{283} - A_{320})_U / V(A_{283} - A_{320})_{5}$$

in which C is the concentration, in µg per mL, of USP Idoxuridine RS in the Standard preparation; V is the volume, in mL, of Ophthalmic Solution taken; and the parenthetic expressions are the differences in the absorbances of the two solutions at the wavelengths indicated by the subscripts, for the Solution (U) and the *Standard preparation* (S), respectively.

# Ifosfamide



- C<sub>7</sub>H<sub>15</sub>Cl<sub>3</sub>N<sub>2</sub>O<sub>2</sub>P 261.09 2H-1,3,2-Oxazaphosphorin-2-amine,N,3-bis(2-chloroethyl)tetrahydro-, 2-oxide.
- 3-(2-Chloroethyl)-[(2-chloroethyl)amino]tetrahydro-2H-1,3,2-oxaza-phosphorine 2-oxide [3778-73-2].

» Ifosfamide contains not less than 98.0 percent and not more than 102.0 percent of C<sub>7</sub>H<sub>15</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>2</sub>P.

Caution-Great care should be taken in handling Ifosfamide, as it is a potent cytotoxic agent and suspected carcinogen.

Packaging and storage—Preserve in tight containers at a temper-ature not exceeding 25°.

Labeling—Where it is intended for use in preparing injectable dosage forms, the label states that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms. USP Reference standards (11)-USP Endotoxin RS. USP Ifosfamide RS.

Identification-

Infrared Absorption (197K) A:

B: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that of the Standard preparation, both relative to the internal standard, as obtained in the Assay.

**pH** (791): between 4.0 and 7.0 in a solution (1 in 10).

Water, Method I (921): not more than 0.3%.

Heavy metals, Method I (231): not more than 0.002%. Ionic chloride-

Standard sodium chloride solution-Transfer about 118.7 mg of sodium chloride, accurately weighed, to a 200-mL volumetric flask, dissolve in and dilute with water to volume, and mix. This solution contains 360 ppm of ionic chloride.

Procedure-Pipet 10 mL of Standard sodium chloride solution into a beaker, and add 90 mL of water and 10 mL of acetic acid. Titrate with 0.01N silver nitrate VS (prepared fresh daily), determining the endpoint potentiometrically using silver and silver-silver chloride electrodes. Record the volume,  $V_1$ , of 0.01 N silver nitrate VS consumed. Transfer about 2.0 g of Ifosfamide, accurately weighed, into a beaker, and add 90 mL of water and 10 mL of acetic acid. Pipet 10 mL of *Standard sodium chloride solution* into the acid. Fiper 10 hill of standard solution controls solution into the beaker, and stir, if necessary, until solution is complete. Titrate with 0.01 N silver nitrate VS as directed above, and record the volume,  $V_{2}$ , of 0.01 N silver nitrate VS consumed. Calculate the difference in volume,  $V_{1}$  of 0.01 N silver nitrate VS consumed between the two determinations by subtracting  $V_{1}$  from  $V_{2}$ : a difference of not more bland. than 1.0 mL corresponding to not more than 0.018% of ionic chloride is found.

#### Chloroform-insoluble phosphorus-

(Solution A). Cautiously add 75 mL of sulfuric acid to 100 mL of water, cool to room temperature, and dilute with water to 200.0 mL (Solution B). Mix Solution A and Solution B to obtain Ammonium molybdate solution.

Hydroquinone solution-Dissolve 0.5 g of hydroquinone in 100 mL of water, and add one drop of concentrated sulfuric acid. [NOTE-

When this solution darkens, discard it and prepare fresh.] Sodium sulfite solution—Prepare a solution of sodium sulfite in water having a concentration of 200 mg per mL. [NOTE—Prepare fresh at the time of use.]

Phosphorus stock solution—Transfer 0.1824g of monobasic potassium phosphate, accurately weighed, to a 1000-mL volument flask, dissolve in and dilute with water to volume, and mix. Phosphorus intermediate solution—Transfer 10.0 mL of Phos

phorus stock solution to a 100-mL volumetric flask, dilute with water

photo a discrete and mix. Prepare this solution fresh on the day of use, Phosphorus standard solution—Transfer 10.0 mL of Phosphoru intermediate solution to a 100-mL volumetric flask, dilute with water and the solution to a 100-mL volumetric flask, dilute with water and the solution to a 100-mL volumetric flask, dilute with water and the solution to a 100-mL volumetric flask, dilute with water and the solution to a 100-mL volumetric flask, dilute with water and the solution to a 100-mL volumetric flask, dilute with water and the solution to a 100-mL volumetric flask, dilute with water and the solution to a 100-mL volumetric flask. to volume, and mix.

Test preparation—Transfer I g of Ifosfamide, accurately weighed to a 100-mL volumetric flask, dissolve in 50 mL of water, dilute with water to volume, and mix. Transfer 10.0 mL of this solution to separatory funnel, and add 5 mL of water. Add 15 mL of chloroform shake vigorously for 30 seconds, allow the layers to separate an drain, and discard the lower chloroform layer. Repeat this extracting four times, each time with 15 mL of chloroform, discarding the chloroform layer after each extraction. Transfer the aqueous portion to a conical flask, wash the separatory funnel with two 5-mL portion of water, and collect all the aqueous washings in the same flask. Ad 3 mL of sulfuric acid, and heat under a hood until white fumes appear Remove the flask from the heat, and with swirling, add 0.6 mL hydrogen peroxide. Heat until white fumes reappear. If the solution not colorless, repeat additions of hydrogen peroxide followed the heating until all color is gone. Cool to room temperature, add 25 m of water, and cautiously add 10 mL of ammonium hydrox solution. Cool to room temperature, add 2 drops of phenolphthal TS, and then add hydrochloric acid dropwise until all pink color h disappeared. Transfer the contents of the flask to a 100-mL flag dilute with water to volume, and mix. Blank solution-To 3 mL of sulfuric acid in a second conical fi

adding 0.6 mL of hydrogen peroxide, proceed as directed for the te preparation, beginning with "Heat until white fumes reappear." Procedure—Transfer 15.0 mL each of the Test preparation, Blank solution, and the Phosphorus standard solution to the separate 25-mL volumetric flasks. Add 2.5 mL of Ammonia methode achieves to acab of the Sanka with a different solution to the molybdate solution to each of the flasks, swirl, and allow to stand about 30 seconds. To each of the three flasks in order, rapidly add 2 mL each of *Hydroquinone solution* and *Sodium sulfite solution* Dilute the contents of each flask with water to volume, mix, and and the flasks to stand for 30 minutes. Concomitantly determine absorbances of the solutions obtained from the Test preparation the Phosphorus standard solution in 1-cm cells at the wavelength maximum absorbance at about 730 nm, with a suitable spectrop tometer, using the solution obtained from the *Blank solution* as blank. Calculate the percentage of chloroform-insoluble phosphore in the portion of Ifosfamide taken by the formula:

$$100(C/W)(A_{11}/A_{2})$$

in which C is the concentration, in  $\mu$ g per mL, of phosphorus in Phosphorus standard solution, W is the weight, in mg, of Ifosfan taken, and  $A_U$  and  $A_s$  are the absorbances from the solutions obtain from the *Test preparation* and the *Phosphorus standard solutions* or the solutions of the preparation and the *Phosphorus standard solution* respectively: not more than 0.0415% is found.

Limit of 2-chloroethylamine hydrochloride-Standard solution—Dissolve an accurately weighed quantity of chloroethylamine hydrochloride in N.N-dimethylacetamide, dilute quantitatively, and stepwise if necessary, with the same s to obtain a solution having a known concentration of about 0.025 per mL.

Test solution—Transfer about 100 mg of Ifosfamide, accur weighed, to a flask, add 10.0 mL of N.N-dimethylacetamide. shake until dissolved.

Chromatographic system—The gas chromatograph is equip with a flame-ionization detector and contains a 2-mm ×

column packed with 10 hydroxide on 80- to 1 maintained at a tempera at a temperature of a temperature of about 14 flow rate of about 25 Procedure-Separate Test solution and the Sta record the chromatogram 2-chloroethylamine hyd chloroethylamine hydroc the formula:

which C is the concent hydrochloride in the Sta Hosfamide taken, and  $r_U$ mine peaks obtained from respectively: not more that ide is found.

Other requirements---V sterile, it meets the requirements and states and state intes that Ifosfamide mus be preparation of injectal by Bacterial endotoxins 1 tosfamide fresh daily ar repare the Standard p ultaneously.]

Mobile phase—Prepare and acetonitrile (70:30). I Autability under Chromatu Internal standard solutic ccurately weighed, to a 10 scohol to dissolve. Dilute Standard preparation B, accurately weighed, to mal standard solution, Assay preparation-Tr curately weighed, to a 2. ernal standard solution, Chromatographic system id chromatograph is e 9-mm × 30-cm column t but 1.5 mL per minute. C at record the peak resp solution, R, between ifosf 0, and the relative standar me than 2.0%.

Procedure-Separately in idard preparation and t raph, record the chromat for peaks. Calculate the q

2

which C is the concentratic the Standard preparation the Assay preparation

# <sup>Posfa</sup>mide for Inj

Ifosfamide for Injection cent and not more the ount of C7H15Cl2N2O2

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нс

thylethyl)amino]-2-hydr ide, (-)-. ropoxy]-3,4-dihydro-1( ?7912-14-7].

USA

ntains not less than n 101.0 percente the dried basis.

well-closed containers. > Levobunolol Hydrochie

and 211°, within a range

-19° and -20°. nethanol. solution (1 in 20). t 1g of it in vacuu ving tube at 110° for 4 ho ۱t.

re than 0.1%.

f sodium 1-heptanesulfon ial acetic acid and 1100 le filter having a 1-µm d ents if necessary (see 21)).

accurately weighed qu S in Mobile phase to ob on of about 1.0 mg per m out 100 mg of Levon to a 100-mL volumetrie hase to volume, and mix Chromatography (621)) ith a 254-nm detector an s packing L1. The flow graph the Standard prepa graph the Standard prepared sected for Procedure: the e lyte peak is not less that r, k', for levobunolol is b inalyte peak is not more in or replicate injections is no

al volumes (about 20 µL) y preparation into the draw and measure the area re-iantity, in mg, of  $C_{17}H_{25}N_{17}$ ochloride taken by the for

,/rs),

mg per mL, of USP Leve preparation; and ru and rs 1 the Assay preparation

evobunolol Hydrochloride Ophthalmic Solution mins not less than 90.0 percent and not more than 0 percent of the labeled amount of  $C_{17}H_{25}NO_3 \cdot HCl$ .

ging and storage—Preserve in tight containers. Reference standards (11)—USP Levobunolol Hydrochloride

infication—The retention time of the major peak in the matogram of the Assay preparation corresponds to that of the peak in the chromatogram of the Standard preparation, as ed in the Assay.

interobial effectiveness (51): meets the requirements.

ty (71)—It meets the requirements when tested as directed for brane Filtration under Test for Sterility of the Product to be hined.

(191): between 5.5 and 7.5.

28

Jution

bile phase—Dissolve 990 mg of sodium 1-heptanesulfonate in L of water, add 10 mL of glacial acetic acid and 1100 mL of mol, mix, pass through a suitable filter having a 1-µm or finer ty, and degas. Make adjustments if necessary (see System bility under Chromatography (621)). indard preparation—Dissolve an accurately weighed quantity of

Levobunolol Hydrochloride RS in *Mobile phase* to obtain a ion having a known concentration of about 0.1 mg per mL. ay preparation—Dilute an accurately measured volume of falmic Solution quantitatively, and stepwise if necessary, with the phase to obtain a solution containing about 0.1 mg of molel hydrochloride per m<sup>2</sup>. olol hydrochloride per mL.

omatographic system (see Chromatography (621))—The chromatograph is equipped with a 254-nm detector and a 4-30-cm column that contains packing L1. The flow rate is 5 mL per minute. Chromatograph the Standard preparation, and the peak responses as directed for Procedure: the column by determined from the analyte peak is not less than 1000 tical plates; the capacity factor, k', for levobunolol is between 1.4; the tailing factor for the analyte peak is not more than 2.6; relative standard deviation for replicate injections is not more 5%.

edure—Separately inject equal volumes (about 30 µL) of the preparation and the Assay preparation into the chromat-record the chromatograms, and measure the area responses major peaks. Calculate the quantity, in mg, of  $C_{17}H_{23}NO_3 \cdot HCl$  mL of the Ophthalmic Solution taken by the formula:

#### $(L/D)(C)(r_u/r_s),$

L is the labeled amount, in mg, of levobunolol hydrochloride mL of the Ophthalmic Solution; D is the concentration, in mg of levobunolol hydrochloride in the Assay preparation, in the labeled quantity per mL and the extent of dilution; C is returnion, in mg per mL, of USP Levobunolol Hydrochloride the Standard preparation; and  $r_{U}$  and  $r_{s}$  are the peak area s obtained from the Assay preparation and the Standard ion, respectively.

# 

C<sub>7</sub>H<sub>15</sub>NO<sub>3</sub> 161.20

- (R)-3-Carboxy-2-hydroxy-N,N,N-trimethyl-1-propanaminium hydroxide, inner salt.
- (R)-(3-Carboxy-2-hydroxypropyl)trimethylammonium hydroxide, inner salt [541-15-1].

» Levocarnitine contains not less than 97.0 percent and not more than 103.0 percent of C7H15NO3, calculated on the anhydrous basis.

Packaging and storage-Preserve in tight containers.

USP Reference standards (11)-USP Levocarnitine RS. Identification, Infrared Absorption (197K)—The test specimen and the Reference Standard are dried previously in vacuum at  $50^{\circ}$  for 5 hours

Specific rotation (781S): between -29° and -32°.

Test solution: 100 mg per mL, in water.

pH (791): between 5.5 and 9.5 in a solution (1 in 20). Water content (921): not more than 4.0%.

Residue on ignition (281): not more than 0.5%.

Chloride (221)—A 0.090-g portion shows no more chloride than corresponds to 0.50 mL of 0.020 N hydrochloric acid (0.4%).

Limit of potassium-[NOTE-The Standard solution and the Test solutions may be modified, if necessary, to obtain solutions of suitable concentrations, adaptable to the linear or working range of the instrument.]

Standard solution—Transfer 5.959 g of potassium chloride, previously dried at 105° for 2 hours and accurately weighed, to a 250-mL volumetric flask, dilute with water to volume, and mix. This solution contains 12.5 mg of potassium per mL. Dilute an accurately measured volume of this solution quantitatively, and stepwise if necessary, with water to obtain a solution containing  $31.25 \ \mu g$  of potassium per mL.

Test solutions-Transfer 62.5 mg of Levocarnitine to a 100-mL volumetric flask, dissolve in and dilute with water to volume, and mix to obtain a stock solution. To three separate 25-mL volumetric flasks add 0, 2.0, and 4.0 mL of the *Standard solution*. To each flask add 20.0 mL of the stock solution, dilute with water to volume, and mix. These solutions contain 0 (Test solution A), 2.5 (Test solution B), and 5.0 (Test solution C) μg per mL of potassium. Procedure—Concomitantly determine the absorbances of the Test

solutions at the potassium emission line at 766.7 nm with a suitable solutions at the potassian emission line at 760.7 fm with a surface atomic absorption spectrophotometer (see Spectrophotometry and Light-Scattering (851)) equipped with an air-acetylene flame, using water as the blank. Plot the absorbances of the Test solutions versus their contents of potassium, in  $\mu$ g per mL, draw the straight line best fitting the three points, and extrapolate the line until it intercepts the concentration axis. From the intercept determine the amount, in µg, of potassium in each mL of *Test solution A*. Calculate the percentage of potassium in the portion of Levocarnitine taken by multiplying the concentration, in  $\mu$ g per mL, of potassium found in *Test solution A* by 0.2: not more than 0.2% is found.

Limit of sodium-[NOTE-The Standard solution and the Test solutions may be modified, if necessary, to obtain solutions of suitable concentrations, adaptable to the linear or working range of the instrument.]

Standard solution-Transfer 6.355 g of sodium chloride, previously dried at 105° for 2 hours and accurately weighed, to a 250-mL volumetric flask, dilute with water to volume, and mix. This solution contains 10.0 mg of sodium per mL. Dilute an accurately measured volume of this solution quantitatively, and stepwise if necessary, with water to obtain a solution containing 250  $\mu$ g of sodium per mL.

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Assay preparation-To about 12 mg of Lincomycin Hydrochlo-ride, accurately weighed, add 10.0 mL of *Mobile phase*. Shake by mechanical means for 5 minutes, and sonicate if necessary to effect solution.

Chromatographic system (see Chromatography (621))—The liquid chromatograph is equipped with a 210-nm detector and a 4.6-mm  $\times$  25-cm column that contains 5- $\mu$ m packing L7 and is maintained at a temperature of 46°. The flow rate is about 1 mL per minute. Chromatograph the Standard preparation, and record the responses as directed for Procedure: the tailing factor for the main lincomycin peak is not more than 1.3; the column efficiency determined from the main lincomycin peak is not less than 4000 theoretical plates; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure-Separately inject equal volumes (about 20 µL) of the Standard preparation and the Assay preparation into the chromat-ograph, record the chromatograms, and measure the areas for the major peaks. The relative retention times are about 0.5 for lincomycin B and 1.0 for lincomycin. Calculate the quantity, in  $\mu$ g, of lincomycin (C<sub>18</sub>H<sub>34</sub>N<sub>2</sub>O<sub>6</sub>S) in each mg of the Lincomycin Hydrochloride taken by the formula:

#### $10(CP/W)(r_u/r_s),$

in which C is the concentration, in mg per mL, of USP Lincomycin Hydrochloride RS in the *Standard preparation*; P is the designated potency, in  $\mu$ g of lincomycin per mg, of USP Lincomycin Hydrochloride RS; W is the weight, in mg, of the portion of Lincomycin Hydrochloride taken to prepare the Assay preparation; and  $r_{U}$  and  $r_{s}$  are the lincomycin peak responses obtained from the Assay preparation and the Standard preparation, respectively.

# Lincomycin Hydrochloride Capsules

» Lincomycin Hydrochloride Capsules contain an amount of C<sub>18</sub>H<sub>34</sub>N<sub>2</sub>O<sub>6</sub>S · HCl · H<sub>2</sub>O equivalent to not less than 90.0 percent and not more than 120.0 percent of the labeled amount of lincomycin (C<sub>18</sub>H<sub>34</sub>N<sub>2</sub>O<sub>6</sub>S).

Packaging and storage-Preserve in tight containers.

USP Reference standards (11)-USP Lincomycin Hydrochloride RS.

Dissolution (711)— Medium: water; 500 mL. Apparatus 1: 100 rpm.

Time: 45 minutes.

Procedure-Filter a portion of about 20 mL of the solution under test. Transfer about 5 mL of the eluant into a small test tube, and add  $250~\mu L$  of 0.01 M sodium sulfate internal standard solution. Evaporate until dry using a vacuum centrifuge. Add 10.0  $\mu L$  of water to the precipitate and place on a vortex mixer until all solid material is dissolved. Transfer this solution to a capillary tube, place it in a Raman spectrometer, and obtain the Raman spectrum using suitable instrumental conditions (see Spectrophotometry and Light-Scattering (851)). Integrate the Raman intensity, applying baseline corrections, between 660 cm<sup>-1</sup> and 720 cm<sup>-1</sup>. Divide this result by the integrated intensity between 966 cm<sup>-1</sup> and 994 cm<sup>-1</sup>. Determine the amount of  $C_{18}H_{34}N_2O_6S$  dissolved in comparison with an aqueous Standard solution having a known concentration of USP Lincomycin Hydrochloride RS.

Tolerances—Not less than 75% (Q) of the labeled amount of  $C_{18}H_{34}N_2O_6S$  is dissolved in 45 minutes.

Uniformity of dosage units (905): meet the requirements. Water, Method I (921): not more than 7.0%.

Assay

Mobile phase, Standard preparation, and Chromatographic system—Proceed as directed in the Assay under Lincomycin Hydrochloride.

Assay preparation-Remove, as completely as possible, the contents of not less than 10 Capsules, taking care to prevent capsule shell fragments from being combined with the capsule contents and to remove any shell fragments from the contents. Weigh and mix the combined contents, and transfer an accurately weighed portion of the

powder, equivalent to about 50 mg of lincomycin, to a suitable container. Add 50.0 mL of *Mobile phase*, and shake by mechanical means for 5 minutes. Use the solution thus obtained as the *Assay* preparation.

Procedure—Proceed as directed for *Procedure* in the Assay under Lincomycin Hydrochloride. Calculate the quantity, in mg, of lincomycin ( $C_{18}H_{34}N_2O_6S$ ) in the portion of Capsule contents taken by the formula:

 $(CP/20)(r_{\rm U}/r_{\rm S}),$ 

in which the terms are as defined therein.

# **Lincomycin Injection**

» Lincomycin Injection contains an amount of Lincomycin Hydrochloride in Water for Injection equivalent to not less than 90.0 percent and not more than 120.0 percent of the labeled amount of lincomycin (C<sub>18</sub>H<sub>34</sub>N<sub>2</sub>O<sub>6</sub>S). It contains benzyl alcohol as a preservative.

Packaging and storage—Preserve in single-dose or in multiple-dose containers, preferably of Type I glass.

USP Reference standards (11)-USP Endotoxin RS. USP Lincomycin Hydrochloride RS.

Bacterial endotoxins (85)-It contains not more than 0.5 USP Endotoxin Unit per mg of lincomycin.

Sterility (71)-It meets the requirements when tested as directed for Membrane Filtration under Test for Sterility of the Product to be Examined.

pH (791): between 3.0 and 5.5.

Particulate matter (788): meets the requirements for small volume injections.

Other requirements-It meets the requirements under Injections  $\langle 1 \rangle$ .

Assay

Mobile phase, Standard preparation, and Chromatographic ystem—Proceed as directed in the Assay under Lincomyce Hydrochloride.

Assay preparation-Transfer an accurately measured volume Injection, equivalent to about 600 mg of lincomycin, to a 50-ml volumetric flask, dilute with *Mobile phase* to volume, and mar Transfer 2.0 mL of this solution to a 25-mL volumetric flask, dilute

with Mobile phase to volume, and mix. Procedure—Proceed as directed for Procedure in the Assay under Lincomycin Hydrochloride. Calculate the quantity, in mg. lincomycin (C<sub>19</sub>H<sub>34</sub>N<sub>2</sub>O<sub>6</sub>S) in each mL of the Injection taken by the formula:

## $0.625(CP/V)(r_u/r_s),$

in which V is the volume, in mL, of Injection taken, and the other terms are as defined therein.

# Lincomycin Hydrochloride Soluble Powder

» Lincomycin Hydrochloride Soluble Powder contai an amount of Lincomycin Hydrochloride equivalent not less than 90.0 percent and not more than 110 percent of the labeled amount of lincomy (C18H34N2O6S).

USP 28

Packaging and stors Labeling-Label it to **USP** Reference stan

dentification-The chromatogram of the chromatogram of the . Minimum fill (755): Water, Method I (92)

Assav

Mobile phase and the Assay under Lin Standard preparatic SP Lincomycin Hy plution having a kno Assay preparation contents, and transfer wder, equivalent to 100-mL volumetric wirl to dissolve. Dil transfer 25.0 mL of Transfer 25.0 mL o. hask, dilute with Mob. Procedure-Proceec H<sub>34</sub>N<sub>2</sub>O<sub>6</sub>S) in the p

which the terms are

# Lincomycin C

onograph under thi Gurrent monograph 1

Lincomycin Or ncomycin hydro quivalent to not 1 n 120.0 percent  $C_{18}H_{34}N_2O_6S$ , and reservatives, and :

ckaging and storag SP Reference stand

formity of dosage FOR ORAL SOLUTIO meets the requirement liverable volume (6 (791): between 3

Mobile phase, Star. Mem—Proceed as c drochloride.

Assay preparational Solution, freshly r out 100 mg of lincorr a precipitate forms. 90 seconds, add 10.0 as for 10 minutes.

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relative response factor,  $F_{min}$  of equal weights of toluene and methyl iodide taken by the formula:

#### 0 .... / A .....

in which  $Q_{mi}$  is the quantity ratio of methyl iodide to toluene in the Standard preparation, and  $A_{mi}$  is the peak area ratio of the methyl iodide to toluene obtained from the Standard preparation.

Procedure-Inject about 2 µL of the upper layer of the Assay preparation into the gas chromatograph, and record the chromatogram. Calculate the percentage of methoxy in the Methylcellulose taken by the formula:

#### $2(31/142)F_{ini}A_{unui}(W_i/W_u),$

in which 31/142 is the ratio of the formula weights of methoxy and methyl iodide;  $F_{m}$  is defined under *Calibration*,  $A_{um}$  is the ratio of the area of the methyl iodide peak to that of the toluene peak obtained from the *Assay preparation*;  $W_i$  is the weight, in g, of toluene in the *Internal standard solution*; and  $W_u$  is the weight, in g, of *Astherical standard solution*; and  $W_u$  is the weight, in g, of Methylcellulose taken for the Assay.

# Methylcellulose Ophthalmic Solution

» Methylcellulose Ophthalmic Solution is a sterile solution of Methylcellulose. It contains not less than 85.0 percent and not more than 115.0 percent of the labeled amount of methylcellulose. It may contain suitable antimicrobial, buffering, and stabilizing agents.

Packaging and storage-Preserve in tight containers.

Identification-It responds to Identification tests B and C under Methylcellulose.

Sterility (71): meets the requirements.

pH (791): between 6.0 and 7.8.

Assay—To boiling flask A, as described under Methoxy Determina-tion (431), pipet a quantity of Ophthalmic Solution, equivalent to 50 mg of methylcellulose. Evaporate on a steam bath to dryness, cool the flask in an ice bath, add the specified amount of hydriodic acid, and proceed as directed under *Methoxy Determination* (431). Each mL of 0.1 N sodium thiosulfate is equivalent to 1.753 mg of methylcellulose.

# **Methylcellulose Oral Solution**

» Methylcellulose Oral Solution is a flavored solution of Methylcellulose. It contains not less than 85.0 percent and not more than 115.0 percent of the labeled amount of methylcellulose.

Packaging and storage-Preserve in tight, light-resistant containers, and avoid exposure to direct sunlight and to excessive heat. Avoid freezing.

Identification—It responds to Identification tests B and C under Methylcellulose

Microbial limits (61)—Its total aerobic microbial count does not exceed 100 cfu per mL, and it meets the requirements of the test for the absence of *Escherichia coli*.

Alcohol content, Method II (611): between 3.5% and 6.5% of C2H3OH.

Assay-To boiling flask A, as described under Methoxy Determination (431), transfer an accurately measured volume of Oral Solution, equivalent to 50 mg of methylcellulose. Evaporate on a steam bath to dryness, cool the flask in an ice bath, add the specified amount of (431). Each mL of 0.1 N sodium thiosulfate is equivalent to 1.753 mg of methylcellulose.

## **Methylcellulose Tablets**

» Methylcellulose Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of methylcellulose.

Packaging and storage-Preserve in well-closed containers. Identification-Add the residue obtained in the Assay to 50 mL of water: the solution responds to the Identification tests under Methylcellulose.

Disintegration (701): 30 minutes.

Uniformity of dosage units (905): meet the requirements. Assay-Weigh and finely powder not less than 20 Tablets. Weigh accurately a portion of the powder, equivalent to about 500 mg of methylcellulose, and transfer to a tared, fine fritted-glass, low-for 30-mL crucible having a fitted crucible lid. Add 20 mL of alcohol and macerate the solid for about 5 minutes, mixing intermittently wind a glass stirring rod. Repeat the extraction with ten consecutive 10 mL portions of alcohol. Test for completeness of extraction by evaporating the last alcohol extract on a steam bath to drynes, taking up the residue in about 1 mL of water, and adding this to 5 mL of hot alkaline cupric tartrate TS (no red precipitate of cuprous oxide is formed within 5 minutes). If a precipitate is formed, continue we the alcohol extractions until the test is negative. Wash the complete extracted residue with a 10-mL portion of ether, using suction to draw off the liquid. Dry the residue in the crucible in a drying over at 10 to constant weight. Weigh the crucible with the crucible lid in ph The weight of residue is the weight of methylcellulose present in a portion of powdered Tablets taken.

### Methyldopa

 $C_{10}H_{13}NO_4 \cdot 1\frac{1}{2}H_2O = 238.24$ L-Tyrosine, 3-hydroxy-a-methyl-, sesquihydrate. L-3-(3,4-Dihydroxyphenyl)-2-methylalanine sesquihydrate [41372-08-1]. Anhydrous 211.22 [555-30-6].

» Methyldopa contains not less than 98.0 percent and ne more than 101.0 percent of  $C_{10}H_{13}NO_4$ , calculated on the analysis basis anhydrous basis.

Packaging and storage-Preserve in well-closed, light-resi containers.

USP Reference standards (11)—USP Methyldopa RS. USP 34 Methylmethyldopa RS.

Identification-

A: Infrared Absorption (197M). B: Ultraviolet Absorption (197U)-

Solution: 40 µg per mL. Medium: 0.1 N hydrochloric acid. Absorptivities at 280 nm, calculated on the anhydrous basis, do

differ by more than 3.0%. C: To 10 mg add 0.15 mL of a solution of ninhydrin in suff C: To 10 mg add 0.15 mL of a solution of ninhydrn in su acid (1 in 250): a dark purple color is produced within 5 m minutes. Add 0.15 mL of water: the color changes to pale brown vellow.

Specific rotation (781S): between  $-25^{\circ}$  and  $-28^{\circ}$ . Test solution: 44 mg per mL, in a solvent that is a solution aluminum chloride in water (2 in 3) which previously has been up with activated charcoal, filtered, and adjusted with 0.25 N so hydroxide to a pH of 1.5.

USP 28

2.0

bl

didity-Dissolve 1.0 g in at, add 1 drop of methy wdroxide to a yellow endr nater, Method I (921): t sidue on ignition (281): wy metals, Method II ( mit of 3-O-methylmethy Developing solvent—Mix is by volume of glacial er. Prepare this mixture Chromatographic platee with a suitable grade of Developing solvent. W p of the plate. Dry with th Spray solution 1—Dissolv N hydrochloric acid (Solu 50 mL of water (Solution . Solution B (Spray solution -Solution B (Spray solution -Spray solution 2-Dissolve

r, and mix.

Test solution-Dissolve 1( Standard solution—Dissol parts in methanol, and dilu and solution having a ku Procedure—Apply 20 µL rements and 10 µL of the whic plate, so that the spot when front has moved about the front has moved about the from the chamber, and ( fill no odor of acetic acid is j which, and evenly spray win be is uniformly soaked dow plate in a horizontal positi the aid of a current of war acceptible). Place the plate *Spray solution 2* until aspray). The major methyl methyleserer and a second ge background at an R<sub>F</sub> bylmethyldopa spot is dark bout 0.65. The area and in from the Test solution a dard solution (0.5%).

ganic volatile impurities, /

olvent-Use dimethyl sulfo -Dissolve about 200 mg 25 mL of glacial acetic acid perature, and add 0.1 mL mitrile. Titrate with 0.1 N p form a blank determination, a mL of 0.1 N perchloric  $H_{10}NO_4$ .

# ethyldopa Oral S

ethyldopa Oral Suspen dethyldopa. It contains ng agents, and prese ose. It contains not le than 110.0 percent II3NO4.

ging and storage-Preserv re at a temperature not ex-Reference standards (1 Ppa-glucose Reaction Pre

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# Naphazoline Hydrochloride Nasal Solution

» Naphazoline Hydrochloride Nasal Solution is a solution of Naphazoline Hydrochloride in water adjusted to a suitable pH and tonicity. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of Naphazoline Hydrochloride  $(C_{14}H_{14}N_2 \cdot HCI).$ 

Packaging and storage-Preserve in tight, light-resistant containers. USP Reference standards (11)-USP Naphazoline Hydrochloride RS

Identification-The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that of the Standard preparation as obtained in the Assay.

Assay

Mobile phase—Dissolve 1.1 g of sodium 1-heptanesulfonate in about 400 mL of water. Add 250 mL of acetonitrile and 10 mL of glacial acetic acid, dilute with water to 1000 mL, and mix. Sonicate for 10 minutes, filter, and degas to obtain a solution having a pH of about 3.5. Make adjustments if necessary (see System Suitability

under *Chromatography* (621)). *Standard preparation*—Dissolve an accurately weighed quantity of USP Naphazoline Hydrochloride RS in water, and dilute quantita-tion of the standard preparation o

Use require regulation of about 250  $\mu$ g per mL. Assay preparation—Pipet a volume of Nasal Solution, equivalent to about 25 mg of naphazoline hydrochloride, into a 100-mL volumetric flask, dilute with water to volume, and mix.

Chromatographic system (see Chromatography (621))-The liquid chromatograph is equiped with a 280-nm detector and a 4-mm  $\times$  30-cm column that contains packing L11. The flow rate is about 2 mL per minute. Chromatograph the *Standard preparation*, and record the peak responses as directed under Procedure: the tailing factor for the naphazoline hydrochloride peak is not more than 2.0, and the relative standard deviation for replicate injections is not more than 1.5%.

Procedure-Separately inject equal volumes (about 15 µL) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of  $C_{14}H_{14}N_2 \cdot HCl$  in each mL of the Nasal Solution taken by the formula:

#### $0.1(C/V)(r_u/r_s),$

in which C is the concentration, in  $\mu$ g per mL, of USP Naphazoline Hydrochloride RS in the *Standard preparation*, V is the volume, in mL, of Nasal Solution taken, and  $r_U$  and  $r_5$  are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.

# Naphazoline Hydrochloride Ophthalmic Solution

» Naphazoline Hydrochloride Ophthalmic Solution is a sterile, buffered solution of Naphazoline Hydrochloride in water adjusted to a suitable tonicity. It contains not less than 90.0 percent and not more than 115.0 percent of the labeled amount of Naphazoline Hydrochloride (C14H14N2 · HCl). It contains a suitable preservative.

Packaging and storage-Preserve in tight containers

USP Reference standards (11)-USP Naphazoline Hydrochloride RS

Identification-Place in a separator a volume of Ophthalmic Solution, equivalent to about 25 mg of naphazoline hydrochloride, add 5 mL of 1 N sodium hydroxide caturate w

and extract with two 25-mL portions of ether. Wash the ether se with 5 mL of water, pass the ether through a small paper evaporate the filtrate to about 5 mL, transfer the residual solution 10- to 15-mL beaker, allow to evaporate spontaneously, and de residue at 80° for 1 hour: the naphazoline so obtained melts be 115° and 120° when determined as directed for *Class la* 

Melting Range or Temperature (741). Sterility (71): meets the requirements.

pH (791): between 5.5 and 7.0.

Assay

Phosphate buffer-Transfer 3 g of monobasic potassium pl to a 1-liter volumetric flask, dissolve in 1000 mL of water and of triethylamine, and mix. Adjust with phosphoric acid to a ph and mix

Mobile phase-Prepare a filtered and degassed mixin Phosphate buffer and acetonitrile (80:20). Make adjustm

Increasing the set of Solution having a known concentration of about 0.05 mg per, Assay preparation—Transfer an accurately measured volu Ophthalmic Solution, equivalent to about 5.0 mg of naph hydrochloride, to a 100-mL volumetric flask, dissolve in and with Mobile phase to volume, and mix.

Chromatographic system (see Chromatography (621)) liquid chromatograph is equipped with a 285-nm detector 4.6-mm × 15-cm column that contains packing L11. The flow 4.0-Init X 19-chi column that contains packing L11. The now about 1.5 mL per minute. The column temperature is mainta 40°. Chromatograph the *Standard preparation*, and record the responses as directed under *Procedure*: the column efficiency less than 5000 theoretical plates, the tailing factor is not not 2.0, and the relative standard deviation for replicate injection more than 2.0%

Procedure—Separately inject equal volumes (about 10 µL) Standard preparation and the Assay preparation into the cograph, record the chromatograms, and measure the responses major peaks. Calculate the quantity, in mg, of C14H14N2 HC portion of Ophthalmic Solution taken by the formula:

# $100C(r_{v}/r_{s}),$

in which C is the concentration, in mg per mL, of USP Naph Hydrochloride RS in the *Standard preparation*, and  $r_0$  and  $r_0$  peak responses obtained from the Assay preparation Standard preparation, respectively.

# Naphazoline Hydrochloride and **Pheniramine Maleate Ophthalmic** Solution

» Naphazoline Hydrochloride and Pheniramine Ophthalmic Solution is a sterile, buffered solu Naphazoline Hydrochloride and Pheniramine Ma water adjusted to a suitable tonicity. It contains than 90.0 percent and not more than 110.0 percent labeled amount of naphazoline hydrochl ( $C_{14}H_{14}N_2$ ·HCl) and pheniramine ma  $(C_{16}H_{20}N_2 \cdot C_4H_4O_4)$ . It contains a suitable present

Packaging and storage—Preserve in tight containers, and temperature between 20° and 25°, protected from light. USP Reference standards (11)—USP Naphazoline Hydra RS. USP Pheniramine Maleate RS. Identification-

A: Proceed as directed in the following thin-layer graphic procedure.

Naphazoline hydrochloride standard solution-Dissol tity of USP Naphazoline Hydrochloride RS in water,

USP

miramine maleate Pheniramine Maleate t 6.0 mg per mL. solution—Dilute, thion with water to obt hazoline hydrochloride

 $dard solution, 10 \ \mu L c$ 30  $\mu L$  of the Test s atographic plate (se mm layer of silica ge in a saturated chroi at system consisting o the solvent front has r Remove the plate i ent front, and allow to in an oven at 105° to heniramine spots are r obtained from the Te n the Naphazoline hy ramine maleate stana The retention times the Assay preparation paration, as obtained in fility (71)—It meets the brane Filtration under mined.

(791): between 5.7 au

uffer solution—Dissolve phate and 20 mL of tri phosphoric acid to a pH mL of solution, and m obile phase—Prepared a cetonitrile (80:20). Ma bility under Chromatog aphazoline hydrochloria tely weighed quantity fobile phase to obtain à se t 0.75 mg per mL.

eniramine maleate st tely weighed quantity le phase to obtain a kno

dard preparationide stock standard soluti standard solution to a the phase to volume, and entrations of naphazol ate of 0.03 and 0.36 mg ay preparation-Transf chloride and 9.0 mg c hetric flask, dilute with  $\Lambda$ pomatographic systemchromatograph is equi  $m \times 15$ -cm column that In  $\times$  15-cm column that 1.5 mL per minute. Christer record the peak respon-tion, *R*, between the na-is not less than 2; the co-reline and phenicarmine 1 zoline and pheniramine the tailing factor is not ative standard deviation f

cedure—Separately injec and preparation and the , record the chromatogra Calculate the quantity,  $N_2 \cdot HCl$ ) in each mL of

25(C

h C is the concentration loride RS in the Stand

Slayback Exhibit 1055, Page 47 of 78 Slayback v. Eye Therapies - IPR2022-00142 USP

ether. Wash the ether soluti through a small paper fil isfer the residual solution in te spontaneously, and dry ne so obtained melts bet directed for Class la un

S.

nobasic potassium phospin 1000 mL of water and 3 m phosphoric acid to a pH of

and degassed mixture ):20). Make adjustments · Chromatography (621)). .ccurately weighed quantity n water, and dilute quar h Mobile phase to obtain of about 0.05 mg per ml curately measured volume, bout 5.0 mg of naphazof : flask, dissolve in and diff

th a 285-nm detector and packing L11. The flow rate temperature is maintained paration, and record the p the column efficiency is ailing factor is not more f for replicate injections

volumes (about 10 µL) of preparation into the chroni measure the responses for mg, of  $C_{14}H_{14}N_2 \cdot HCl$  in by the formula:

#### s),

per mL, of USP Naphazo paration, and ry and rs are Assay preparation and

# oride and )phthalmic

nd Pheniramine Male le, buffered solution | Pheniramine Malean icity. It contains not than 110.0 percent of zoline hydrochlor eniramine male s a suitable preservati

tight containers, and store tected from light. P Naphazoline Hydrochi

ollowing thin-layer chron

d solution-Dissolve & ide RS in water to obt mL.

pheniramine maleate standard solution-Dissolve a quantity of USP Pheniramine Maleate RS in water to obtain a solution containing about 6.0 mg per mL

Test solution—Dilute, if necessary, a volume of Ophthalmic Solution with water to obtain a solution containing about 0.25 mg of maphazoline hydrochloride per mL and 3 mg of pheniramine maleate per mL.

Procedure—Separately apply 5  $\mu$ L of Naphazoline hydrochloride andard solution, 10  $\mu$ L of Pheniramine maleate standard solution, and 30  $\mu$ L of the Test solution to a 20-cm  $\times$  20-cm thin-layer anomatographic plate (see *Chromatography* (621)) coated with a 22-cm layer of silica gel. Allow the spots to dry, then place the tate in a saturated chromatographic chamber, and develop in a followent system consisting of methanol, water, and acetic acid (8:1:1) multi the solvent front has moved to about 1.5 cm from the top of the multi the solvent front has moved to about 1.5 cm from the top of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow to air-dry. Spray with ninhydrin TS, and place in an oven at 105° to visualize the spots. Both the naphazoline and pheniramine spots are purplish grey in color. The  $R_F$  values of the pots obtained from the *Test solution* correspond to those obtained from the Naphazoline hydrochloride standard solution and the Pheniramine maleate standard solution.

**B:** The retention times of the major peaks in the chromatogram of the Assay preparation correspond to those of the Standard preparation, as obtained in the Assay.

sterility (71)—It meets the requirements when tested as directed for Membrane Filtration under Test for Sterility of the Product to be frammed.

**H** (791): between 5.7 and 6.3.

Assay-Buffer solution—Dissolve 14.2 g of anhydrous dibasic sodium hosphate and 20 mL of triethylamine in 1900 mL of water, adjust with phosphoric acid to a pH of  $5.6 \pm 0.1$ , dilute with water to make 000 mL of solution, and mix.

Mobile phase—Prepared a filtered and degassed mixture of Buffer d acetonitrile (80:20). Make adjustments if necessary (see System sitability under Chromatography (621)). Naphazoline hydrochloride stock standard solution—Dissolve an curately weighed quantity of USP Naphazoline Hydrochloride RS

*Mobile phase* to obtain a solution having a known concentration of bout 0.75 mg per mL.

Pheniramine maleate stock standard solution-Dissolve an curately weighed quantity of USP Pheniramine Maleate RS in bobile phase to obtain a known concentration of about 3.00 mg per

Standard preparation—Transfer 1.0 mL of Naphazoline hydro-bloride stock standard solution and 3.0 mL of Pheniramine maleate took standard solution to a 25-mL volumetric flask, dilute with tobile phase to volume, and mix to obtain a solution having known

Hobile phase to volume, and mix to obtain a solution having known foncentrations of naphazoline hydrochloride and pheniramine maleate of 0.03 and 0.36 mg per mL, respectively. Assay preparation—Transfer an accurately measured volume of phthalmic Solution, equivalent to about 0.75 mg of naphazoline idrochloride and 9.0 mg of pheniramine maleate, to a 25-mL unmetric flask, dilute with Mobile phase to volume, and mix. *Chromatographic system* (see *Chromatography* (521))—The uid chromatograph is equipped with a 270-nm detector and a 50 mm  $\times$  15-cm column that contains packing L7. The flow rate is out 1.5 mL per minute. Chromatograph the Standard preparation, d record the peak responses as directed for *Procedure:* the **but** 1.5 mL per minute. Chromatograph the *standara preparation*, and record the peak responses as directed for *Procedure*: the solution, *R*, between the naphazoline peak and the pheniramine ask is not less than 2; the column efficiency, determined from the phazoline and pheniramine peaks, is not less than 750 theoretical ties: the tailing factor is not greater than 2.5 for pheniramine; and relative standard deviation for replicate injections is not more than which is the tailing factor is not greater than 2.5 for pheniramine; and relative standard deviation for replicate injections is not more than which is the standard deviation for replicate injections is not more than which is the standard deviation for replicate injections is not more than which is the standard deviation for replicate injections is not more than which is the standard deviation for replicate injections is not more than which is the standard deviation for replicate injections is not more than which is the standard deviation for replicate injections is not more than which is the standard deviation of the standard deviation of the standard deviation is not be a standard deviation of the standard deviating deviating deviation of the standar

Procedure-Separately inject equal volumes (about 25 µL) of the and ard preparation and the Assay preparation into the chromatograms, and measure the responses for the area. Calculate the quantity, in mg, of naphazoline hydrochloride  $\mathcal{C}_{H_1,N_2}$ . HCI) in each mL of the Ophthalmic Solution taken by the mula: ndard preparation and the Assay preparation into the chromat-

#### $25(C/V)(r_U/r_s),$

which C is the concentration in mg per mL of USP Naphazoline dechloride RS in the *Standard preparation*; V is the volume, in of Ophthalmic solution taken; and  $r_U$  and  $r_s$  are the naphazoline

peak responses obtained from the Assay preparation and the Standard preparation, respectively. Calculate the quantity, in mg, of pheniramine maleate  $(C_{16}H_{20}N_2\cdot C_4H_4O_4)$  in each mL of the Ophthalmic Solution taken by the same formula, changing the terms to refer to pheniramine maleate.

## Naproxen

C14H14O3 230.26

(+)-(S)-6-Methoxy-α-methyl-2-naphthaleneacetic acid [22204-53-1].

» Naproxen contains not less than 98.5 percent and not more than 101.5 percent of C14H14O3, calculated on the dried basis.

Packaging and storage-Preserve in tight containers. USP Reference standards (11)-USP Naproxen RS.

Identification-

A: Infrared Absorption (197K). B: Ultraviolet Absorption (197U)— Solution: 25 μg per mL.

Medium: methanol.

Absorptivities at 271 nm, calculated on the dried basis, do not differ by more than 3%.

Specific rotation (781S): between +63.0° and +68.5°.

Test solution: 10 mg per mL, in chloroform.

**Loss on drying** (731)—Dry it at 105° for 3 hours: it loses not more than 0.5% of its weight.

Heavy metals, Method II (231): 0.002%.

**Chromatographic purity**—Dissolve 100 mg of Naproxen in methanol, and dilute with methanol to 5.0 mL to obtain the *Test solution*. Dissolve a suitable quantity of USP Naproxen RS in methanol to obtain a Standard solution having a known concentration of about 20 mg per mL. Dilute a portion of this solution quantitatively and stepwise with methanol to obtain three *Comparison solutions* having concentrations of 20, 60, and 100  $\mu$ g per mL (0.1%, 0.3%, and 0.5% of the *Standard solution*), respectively. Apply separate 10- $\mu$ L portions of the five solutions to the starting line of a suitable thin-layer chromatographic plate (see Chromatography (621)) coated with a 0.25-mm layer of chromatographic silica gel mixture. Develop the chromatogram in a solvent system consisting of a mixture of toluene, tetrahydrofuran, and glacial acetic acid (30:3:1) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the chamber, mark the solvent front, air-dry, and view under short-wavelength UV light: the  $R_F$  value of the principal spot in the chromatogram of the *Test solution* corresponds to that of the *Standard solution*, and any other spot obtained from the Test solution does not exceed, in size or intensity, the principal spot obtained from the 100-µg-per-mL Comparison solution (0.5%), and the sum of the intensities of any secondary spots, similarly compared, does not exceed 2.0%

Organic volatile impurities, Method V (467): meets the requirements.

Solvent-Use dimethyl sulfoxide.

Assay—Dissolve about 500 mg of Naproxen, accurately weighed, in a mixture of 75 mL of methanol and 25 mL of water that has been previously neutralized to the phenolphthalein endpoint with 0.1 N sodium hydroxide. Dissolve by gentle warming, if necessary, add phenolphthalein TS, and titrate with 0.1 N sodium hydroxide VS. Each mL of 0.1 N sodium hydroxide is equivalent to 23.03 mg of C14H14O3.

Slayback Exhibit 1055, Page 48 of 78 Slayback v. Eye Therapies - IPR2022-00142 ent as directed in ent as directed in the

tracin Zinc

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test (201BNP): mee

ts.

, 20 mL of a mixture lace of methanol in t

itracin-Proceed w in and in the Assay Sulfates and Bacitra

# amethasone

iethasone Sodi ivalent of not le 135.0 percent of e equivalent of n ian 110.0 percent hasone phospha

psible tubes or in the

examethasone RS. U cin Sulfate RS.

ycin under Thin-Lo νP). directed in the Assay rements for the Iden hosphate Cream.

nts. as directed in the As

15 M Phosphate bug and Chromatograp under Dexamethas

ly weighed portion under Dexametha

edure in the Assay Calculate the quant

of dexamethasone phosphate  $(C_{22}H_{30}FO_8P)$  in the portion of am taken by the formula:

 $0.1C(r_u/r_s).$ 

# eomycin Sulfate and Dexamethasone dium Phosphate Ophthalmic Ointment

Neomycin Sulfate and Dexamethasone Sodium hosphate Ophthalmic Ointment is a sterile ointment ontaining Neomycin Sulfate and Dexamethasone dium Phosphate. It contains the equivalent of not s than 90.0 percent and not more than 135.0 percent of e labeled amount of neomycin, and the equivalent of at less than 90.0 percent and not more than 110.0 ercent of the labeled amount of dexamethasone hosphate (C<sub>22</sub>H<sub>30</sub>FO<sub>8</sub>P).

OTE-Where Neomycin Sulfate and Dexamethasone idium Phosphate Ophthalmic Ointment is prescribed Thout reference to the quantity of neomycin or tamethasone phosphate contained therein, a product that and 0.5 mg of neomycin and 0.5 mg of tamethasone phosphate per g shall be dispensed.

ckaging and storage-Preserve in collapsible ophthalmic ointt tubes

**SP Reference standards** (11)—USP Dexamethasone RS. USP mamethasone Phosphate RS. USP Neomycin Sulfate RS.

intification-A: It meets the requirements for neomycin under Thin-Layer atographic Identification Test (201BNP).

B: The Assay preparation, prepared as directed in the Assay for amethasone phosphate, meets the requirements for the Identifi-tion test under Dexamethasone Sodium Phosphate Cream.

rility (71): meets the requirements.

ter, Method I (921): not more than 1.0%, 20 mL of a mixture of them and methanol (7:3) being used in place of methanol in the

thin vessel. the particles—It meets the requirements of the test for Metal particles—It meets the requirements (751).

ry for neomycin—Proceed as directed under Antibiotics— crobial Assays (81), using an accurately weighed portion of malmic Ointment shaken in a separator with about 50 mL of , and extracted with four 20-mL portions of Buffer No. 3. making the aqueous extracts, and dilute with Buffer No. 3 to an mopriate volume to obtain a stock solution. Dilute this stock mion quantitatively and stepwise with *Buffer No. 3* to obtain a *Test* ution having a concentration assumed to be equal to the median level of the Standard.

wy for dexamethasone phosphate— Micohol-aqueous phosphate buffer, 0.05 M Phosphate buffer, bile phase, Standard preparation, and Chromatographic tem-Prepare as directed in the Assay under Dexamethasone dium Phosphate Cream.

stay preparation—Using an accurately weighed portion of malmic Ointment, prepare as directed in the Assay under amethasone Sodium Phosphate Cream.

recedure-Proceed as directed for Procedure in the Assay under ethasone Sodium Phosphate Cream. Calculate the quantity, in for dexamethasone phosphate ( $C_{22}H_{30}FO_8P$ ) in the portion of halmic Ointment taken by the formula:

 $0.1C(r_u/r_s).$ 

#### Official Monographs / Neomycin 1345

# Neomycin Sulfate and Dexamethasone Sodium Phosphate Ophthalmic Solution

» Neomycin Sulfate and Dexamethasone Sodium Phosphate Ophthalmic Solution is a sterile, aqueous solution of Neomycin Sulfate and Dexamethasone Sodium Phosphate. It contains the equivalent of not less than 90.0 percent and not more than 130.0 percent of the labeled amount of neomycin, and the equivalent of not less than 90.0 percent and not more than 115.0 percent of the labeled amount of dexamethasone phosphate  $(C_{22}H_{30}FO_8P)$ . It may contain one or more suitable buffers, dispersants, and preservatives.

NOTE-Where Neomycin Sulfate and Dexamethasone Sodium Phosphate Ophthalmic Solution is prescribed, without reference to the amount of neomycin or dexamethasone phosphate contained therein, a product containing 3.5 mg of neomycin and 1.0 mg of dexamethasone phosphate per mL shall be dispensed.

Packaging and storage-Preserve in tight, light-resistant containers, and avoid exposure to excessive heat.

USP Reference standards (11)---USP Dexamethasone RS. USP Dexamethasone Phosphate RS. USP Neomycin Sulfate RS. Identification-

A: It meets the requirements for neomycin under Thin-Layer Chromatographic Identification Test (201BNP).

B: The Assay preparation, prepared as directed in the Assay for dexamethasone phosphate, meets the requirements for the Identification test under Dexamethasone Sodium Phosphate Cream.

Sterility (71): meets the requirements.

pH (791): between 6.0 and 8.0.

Assay for neomycin-Proceed as directed under Antibiotics-Microbial Assays (81), using an accurately measured volume of Ophthalmic Solution diluted quantitatively and stepwise with Buffer No. 3 to yield a Test Dilution having a concentration assumed to be equal to the median dose level of the Standard (1.0  $\mu$ g of neomycin per mL).

Assay for dexamethasone phosphate— 0.002 M Phosphate buffer—Dissolve 0.57 g of dibasic sodium phosphate in water to obtain 2000 mL of solution. 0.10 M Phosphate buffer—Dissolve 13.80 g of monobasic sodium

phosphate in water to obtain 1000 mL of solution.

Mobile phase-Prepare a suitable filtered mixture of 0.10 M phosphate buffer and acetonitrile (690:310). Make adjustments if necessary (see System Suitability under Chromatography (621)). Standard preparation—Dissolve an accurately weighed quantity of

USP Dexamethasione Phosphate RS in 0.002 M Phosphate buffer to obtain a solution having a known concentration of about 125 µg per mL. Transfer 20.0 mL of this solution to a 100-mL volumetric flask, dilute with 0.002 M Phosphate buffer to volume, mix, and pass through a suitable filter of 1  $\mu m$  or finer porosity. This solution

contains about 25 µg per mL. Assay preparation—Transfer an accurately measured volume of Ophthalmic Solution, equivalent to about 2.5 mg of dexamethasone phosphate, to a 100-mL volumetric flask, slowly dilute with 0.002 M Phosphate buffer to volume, mix, and pass through a suitable filter of 1 µm or finer porosity.

Chromatographic system (see Chromatography (621))—The liquid chromatograph is equipped with a 254-nm detector and a 4-mm  $\times$  30-cm column that contains packing L1. The flow rate is about 1.3 mL per minute. Chromatograph the Standard preparation, and measure the peak responses as directed under Procedure: the column efficiency is not less than 2000 theoretical plates, the capacity factor, K, for the dexamethasone phosphate peak is not less than 1.05, and the relative standard deviation for replicate injections is not more than 2.0%.

-[NOTE-Use peak areas where peak responses are Procedureindicated.] Separately inject equal volumes (about 50 µL) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the areas for the

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major peaks. Calculate the quantity, in mg, of dexamethasone phosphate ( $C_{22}H_{30}FO_3P$ ), in each mL of the Ophthalmic Solution taken by the formula:

#### $0.1(C/V)(r_u/r_s),$

in which C is the concentration, in  $\mu g$  per mL, of USP Dexamethasone Phosphate RS in the *Standard preparation;* V is the volume, in mL, of Ophthalmic Solution taken; and  $r_u$  and  $r_s$  are the dexamethasone phosphate peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively.

# Neomycin Sulfate and Fluocinolone Acetonide Cream

» Neomycin Sulfate and Fluocinolone Acetonide Cream contains the equivalent of not less than 90.0 percent and not more than 135.0 percent of the labeled amount of neomycin, and the equivalent of not less than 90.0 percent and not more than 110.0 percent of the labeled amount of fluocinolone acetonide ( $C_{24}H_{30}F_2O_6$ ).

Packaging and storage—Preserve in collapsible tubes or in tight containers.

USP Reference standards (11)—USP Fluocinolone Acetonide RS. USP Neomycin Sulfate RS.

Identification-

A: It meets the requirements for neomycin under *Thin-Layer* Chromatographic Identification Test (201BNP).

**B:** It meets the requirements for the *Identification* test under *Fluocinolone Acetonide Cream*.

Minimum fill (755): meets the requirements.

Assay for neomycin—Proceed with Cream as directed in the Assay under Neomycin Sulfate Cream.

Assay for fluocinolone acetonide—Proceed with Cream as directed in the Assay under Fluocinolone Acetonide Cream.

# Neomycin Sulfate and Fluorometholone Ointment

» Neomycin Sulfate and Fluorometholone Ointment contains the equivalent of not less than 90.0 percent and not more than 135.0 percent of the labeled amount of neomycin, and not less than 90.0 percent and not more than 110.0 percent of the labeled amount of fluorometholone ( $C_{22}H_{29}FO_4$ ).

Packaging and storage—Preserve in collapsible tubes or in wellclosed containers.

USP Reference standards (11)—USP Fluorometholone RS. USP Neomycin Sulfate RS.

Identification— A: It meets the requirements for neomycin under *Thin-Layer Chromatographic Identification Test* (201BNP).

**B:** The ratios of the retention time of the main peak to that of the internal standard peak obtained from the *Standard preparation* and the *Assay preparation* as directed in the *Assay for fluorometholone* do not differ by more than 2.0%.

Minimum fill (755): meets the requirements.

Water, Method I (921): not more than 1.0%, 20 mL of a mixture of toluene and methanol (7:3) being used in place of methanol in the titration vessel.

Assay for neomycin—Proceed with Ointment as directed in the Assay under Neomycin Sulfate Ointment.

#### Assay for fluorometholone-

Internal standard solution, Mobile solvent, and Standard preparation-Prepare as directed in the Assay under Fluoromethology Cream.

Assay preparation—Transfer an accurately weighed quantity of Ointment, equivalent to about 1 mg of fluorometholone, to a suitable container, add 20.0 mL of *Internal standard solution*, and mix.

Procedure—Treat 20.0 mL each of the Standard preparation and the Assay preparation in the following manner. To each add 10.0 m of hexane, shake for about 15 minutes, then allow the layers separate, and centrifuge, if necessary. Using the lower (acetonibile layer, proceed as directed for Procedure in the Assay und Fluorometholone Cream, beginning with "Using a suitable micn syringe." Calculate the quantity, in mg, of  $C_{22}H_{23}FO_4$  in the portion Ointment taken by the formula:

### $20C(R_u/R_s),$

in which the terms are as defined therein.

# Neomycin Sulfate and Flurandrenolide Cream

» Neomycin Sulfate and Flurandrenolide Cream contain the equivalent of not less than 90.0 percent and not more than 135.0 percent of the labeled amount of neomyc and not less than 90.0 percent and not more than 110 percent of the labeled amount of flurandrenolic  $(C_{24}H_{33}FO_6)$ .

Packaging and storage—Preserve in collapsible tubes or in the containers, protected from light.

USP Reference standards (11)—USP Flurandrenolide RS. U Neomycin Sulfate RS.

Identification-

A: It meets the requirements for neomycin under Thin-Lag Chromatographic Identification Test (201BNP). B: It meets the requirements for the Identification test un

Flurandrenolide Cream.

Minimum fill (755): meets the requirements.

Assay for neomycin—Proceed with Cream as directed in the An under Neomycin Sulfate Ointment.

Assay for flurandrenolide—Proceed with Cream as directed in Assay under Flurandrenolide Cream. Calculate the quantity, in  $m_{C_{24}H_{33}}$ FO<sub>6</sub> in the portion of Cream taken by the formula:

#### $10C(r_u/r_s),$

in which C is the concentration, in mg per mL, of U Flurandrenolide RS in the *Standard preparation*; and  $r_v$  and  $r_h$ the peak responses obtained from the Assay preparation and Standard preparation, respectively.

# Neomycin Sulfate and Flurandrenolide Lotion

» Neomycin Sulfate and Flurandrenolide Lotion com the equivalent of not less than 90.0 percent and not not than 130.0 percent of the labeled amount of neomy and not less than 90.0 percent and not more than 1 percent of the labeled amount of flurandrenol  $(C_{24}H_{33}FO_6)$ .

Packaging and storage—Preserve in tight containers, prof from light.

USP 28

### Reference standards omycin Sulfate RS. attification—

It meets the requirent matographic Identificat. It meets the requirent mandrenolide Cream.

erobial limits (61)—It r ence of Staphylococcus a himum fill (755): meet ny for neomycin—Proc biotics—Microbial Assa tion of Lotion, equivalent 3 to 5 minutes in a high mately measured volume a solution having a conve ccurately measured volu b Buffer No. 3 to obtain a mycin assumed to be e pdard.

ny for flurandrenolidemadrenolide Lotion as di *Cream*. Calculate the fon of Lotion taken by the

which C is the conce andrenolide RS in the S peak responses obtained and preparation, respect

# omycin Sulfate Intment

Neomycin Sulfate hains the equivalent not more than 135.0 mycin, and not less 110.0 percent of th  $c(C_{24}H_{33}FO_6)$ .

niners, protected from lig Reference standards opin Sulfate RS.

It meets the requirer tatographic Identificate It meets the requirer

Method I (921): no me and methanol (7:3)

for neomycin—Proc under Neomycin Sulfa. for flurandrenolideray under Flurandrenolite C<sub>24</sub>H<sub>33</sub>FO<sub>6</sub> in the port

> ich C is the conce renolide RS in the S responses obtained preparation, respec

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Assay for polymyxin B—Proceed as directed under Antibiotics— Microbial Assays (81), using an accurately weighed portion of Cream shaken with about 50 mL of ether in a separator, and extracted with four 25-mL portions of Buffer No. 6. Combine the aqueous extracts, and dilute with Buffer No. 6 to an appropriate volume to obtain a stock solution. Dilute this stock solution quantitatively and stepwise with Buffer No. 6 to obtain a Test Dilution having a concentration assumed to be equal to the median dose level of the Standard (10 Polymyxin B Units per mL). Add to each test dilution of the Standard a quantity of USP Neomycin Sulfate RS, dissolved in Buffer No. 6, to obtain the same concentration of neomycin present in the Test Dilution.

# Neomycin and Polymyxin B Sulfates Solution for Irrigation

» Neomycin and Polymyxin B Sulfates Solution for Irrigation is a sterile, aqueous solution containing the equivalent of not less than 90.0 percent and not more than 130.0 percent of the labeled amounts of neomycin and of polymyxin B. It may contain a suitable preservative.

Packaging and storage-Preserve in tight containers.

Labeling—Label it to indicate that it is to be diluted for use in a urinary bladder irrigation and is not intended for injection.

USP Reference standards (11)—USP Neomycin Sulfate RS. USP Polymyxin B Sulfate RS.

Thin-layer chromatographic identification test  $\langle 201BNP \rangle$ : meets the requirements.

Sterility (71)—It meets the requirements when tested as directed for Membrane Filtration under Test for Sterility of the Product to be Examined.

**pH** (791): between 4.5 and 6.0.

Assay for neomycin and Assay for polymyxin B—Proceed with Neomycin and Polymyxin B Sulfates Solution for Irrigation as directed in the Assay for neomycin and in the Assay for polymyxin B under Neomycin and Polymyxin B Sulfates and Hydrocortisone Otic Solution.

# Neomycin and Polymyxin B Sulfates Ophthalmic Ointment

» Neomycin and Polymyxin B Sulfates Ophthalmic Ointment is a sterile ointment containing Neomycin Sulfate and Polymyxin B Sulfate. It contains the equivalent of not less than 90.0 percent and not more than 130.0 percent of the labeled amounts of neomycin and polymyxin B.

Packaging and storage—Preserve in collapsible ophthalmic ointment tubes.

USP Reference standards (11)—USP Neomycin Sulfate RS. USP Polymyxin B Sulfate RS.

Thin-layer chromatographic identification test  $\langle 201BNP \rangle$ : meets the requirements.

Sterility (71)—It meets the requirements when tested as directed for Membrane Filtration under Test for Sterility of the Product to be Examined.

Minimum fill (755): meets the requirements.

Water, *Method I* (921): not more than 0.5%, 20 mL of a mixture of toluene and methanol (7:3) being used in place of methanol in the titration vessel.

USP 28

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Metal particles—It meets the requirements of the test for Metal Particles in Ophthalmic Ointments (751).

Assay for neomycin and Assay for polymyxin B—Proceed with Ophthalmic Ointment as directed in the Assay for neomycin and in the Assay for polymyxin B under Neomycin and Polymyxin B Sulfates and Bacitracin Zinc Ophthalmic Ointment.

# Neomycin and Polymyxin B Sulfates Ophthalmic Solution

» Neomycin and Polymyxin B Sulfates Ophthalma Solution contains the equivalent of not less than 90, percent and not more than 130.0 percent of the labeled amounts of neomycin and polymyxin B. It may contain one or more suitable buffers, dispersants, irrigants, and preservatives.

Packaging and storage—Preserve in tight containers, and average exposure to excessive heat.

USP Reference standards (11)—USP Neomycin Sulfate RS. U Polymyxin B Sulfate RS.

Thin-layer chromatographic identification test (201BNP): meets the requirements.

Sterility (71)—It meets the requirements when tested as directed Membrane Filtration under Test for Sterility of the Product tak Examined.

pH (791): between 5.0 and 7.0.

Assay for neomycin and Assay for polymyxin B—Proceed w Ophthalmic Solution as directed in the Assay for neomycin and in Assay for polymyxin B under Neomycin and Polymyxin B Sulfates Hydrocortisone Otic Solution.

# Neomycin and Polymyxin B Sulfates and Bacitracin Ointment

» Neomycin and Polymyxin B Sulfates and Bacitra Ointment contains the equivalent of not less than 9 percent and not more than 130.0 percent of the labe amounts of neomycin, polymyxin B, and bacitracin may contain a suitable local anesthetic.

Packaging and storage—Preserve in tight, light-resistant contain preferably at controlled room temperature.

USP Reference standards (11)----USP Bacitracin Zinc RS. Neomycin Sulfate RS. USP Polymyxin B Sulfate RS. Thin-layer chromatographic identification test (201BNP) meets the requirements.

Minimum fill (755): meets the requirements.

Water, Method I (921): not more than 0.5%, 20 mL of a mixin toluene and methanol (7:3) being used in place of methanol titration vessel.

Assay for neomycin and Assay for polymyxin B--Proceed Ointment as directed in the Assay for neomycin and in the Assay polymyxin B under Neomycin and Polymyxin B Sulfate Bacitracin Zinc Ophthalmic Ointment.

Assay for bacitracin—Proceed with Ointment as directed Assay under Bacitracin Ointment.

# omycin and ] citracin Oph

keomycin and Pol thalmic Ointmen mycin Sulfate, Pc antains the equivanot more than 14 peomycin, polymy

aging and storage-

Reference standar pcin Sulfate RS. USI Hayer chromatogra the requirements.

brane Filtration und

mum fill (755): m m, Method I (921): m and methanol (7:

ion vessel.

eles in Ophthalmic C for neomycin and

admic Ointment as di for polymyxin B und racin Zinc Ophthalm y for bacitracin ed in the Assay for b

# omycin and F citracin, and tment

omycin and Poly ocortisone Aceta f not less than 90 at of the labeled d bacitracin, and than 110.0 pe fortisone acetate

containers.

deference standard sortisone Acetate an B Sulfate RS.

It meets the requiret tation Test (201BN The retention time in the chromatogram the chromatogram of by for hydrocortison of for hydrocortison in fill (755): me Method J (921): I and methanol (7:3 byessel.

r neomycin and as directed in the B under Neon Zinc Ophthalmi

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# USP 28

tity, in mg, of lidocation in the formula:

mL, of USP Lidocaine provide the lidocaine provide  $r_s$  are the lidocaine provide aration and the Standard

# 1 B Sulfates and mic Ointment

alfates and Dexamen ains the equivalent not more than 130 ts of neomycin 90.0 percent and e labeled amount

ollapsible ophthalmic d

' Dexamethasone RS. Sulfate RS.

hin-Layer Chromatogra

eak for dexamethasone in a corresponds to that in ion, as obtained in the A

s when tested as directed erility of the Product ar

rements.

an 0.5%, 20 mL of a min d in place of methanol in

ments of the test for

olymyxin B—Proceed, Assay for neomycin and and Polymyxin B Sulface

ueous solution of acetonia tion time of dexamethas

of acetonitrile and method with concentration of about

curately weighed portiout 3 mg of dexamethasi of cyclohexane, and hea [NOTE—If the ointment ar r about 30 seconds, place namedium-porosity sim ice with 10-mL portion pugh the filter, and discar ltrate in a 50-mL beaker, al 10-mL portions of the the 50-mL beaker. Transs umetric flask, with the al l (1:1), dilute with the

thromatography (621)) with a 254-nm detector  $16 \text{-mm} \times 25$ -cm column that contains 5- to 10- $\mu$ m packing L1. The now rate is about 2 mL per minute. Chromatograph the *Standard reparation*, and record the peak response as directed under *rocedure:* the column efficiency is not less than 4000 theoretical lates, and the relative standard deviation for replicate injections is not more than 1.5%.

Procedure—Separately inject equal volumes (about 10  $\mu$ L) of the sundard preparation and the Assay preparation into the chromatorgaph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of C<sub>22</sub>H<sub>29</sub>FO<sub>3</sub> in the motion of Ophthalmic Ointment taken by the formula:

#### $50C(r_u/r_s),$

which C is the concentration, in  $\mu$ g per mL, of USP peramethasone RS in the *Standard preparation*; and  $r_0$  and  $r_s$  are peak responses of the *Assay preparation* and the *Standard reparation*, respectively.

# Neomycin and Polymyxin B Sulfates and Dexamethasone Ophthalmic Suspension

Neomycin and Polymyxin B Sulfates and Dexamethsone Ophthalmic Suspension contains the equivalent of not less than 90.0 percent and not more than 130.0 percent of the labeled amounts of neomycin and folymyxin B, and not less than 90.0 percent and not hore than 110.0 percent of the labeled amount of examethasone. It may contain one or more suitable auffers, stabilizers, preservatives, and suspending perts.

ackaging and storage—Preserve in tight, light-resistant containers a cool place or at controlled room temperature. The containers or idividual cartons are sealed and tamper-proof so that sterility is used at time of first use.

**SP Reference standards**  $\langle 11 \rangle$ —USP Dexamethasone RS. USP teomycin Sulfate RS. USP Polymyxin B Sulfate RS.

initication—Transfer a quantity of Ophthalmic Suspension, invalent to about 2.5 mg of dexamethasone, to a suitable test e, add 5 mL of chloroform, mix, and centrifuge. Apply 25  $\mu$ L of lower chloroform layer and 25  $\mu$ L of a Standard solution of USP examethasone RS in chloroform containing 500  $\mu$ g per mL to a itable thin-layer chromatographic plate (see *Chromatography* 21)) coated with a 0.25-mm layer of chromatographic silica gel. How the spots to dry, and develop the chromatogram in a solvent tem consisting of a mixture of chloroform and diethylamine (2:1) if the solvent front has moved about three-fourths of the length of plate. Remove the plate from the developing chamber, mark the vent front, and allow the solvent to evaporate. Locate the spots on plate by examination under short-wavelength UV light: the  $R_r$ ne of the principal spot obtained from the test solution corresponds that obtained from the Standard solution.

rility (71)—It meets the requirements when tested as directed for mbrane Filtration under Test for Sterility of the Product to be mined.

(791): between 3.5 and 6.0.

biotics—Microbial Assays (81), using an accurately measured ame of Ophthalmic Suspension, freshly mixed and free from air bbles, diluted quantitatively and stepwise with Buffer No. 3 to yield for Dilution having a concentration assumed to be equal to the dian dose level of the Standard.

y for polymyxin B—Proceed as directed for polymyxin B under biotics—Microbial Assays (81), using an accurately measured the of Ophthalmic Suspension, freshly mixed and free from air bles, diluted quantitatively and stepwise with Buffer No. 6 to yield for Dilution having a concentration assumed to be equal to the lian dose level of the Standard. Add to each test dilution of the dard a quantity of USP Neomycin Sulfate RS, dissolved in Buffer No. 6, to obtain the same concentration of neomycin as is present in the Test Dilution.

#### Assay for dexamethasone-

Mobile phase and Chromatographic system—Proceed as directed in the Assay for dexamethasone under Neomycin and Polymyxin B Sulfates and Dexamethasone Ophthalmic Ointment.

Standard preparation—Dissolve an accurately weighed quantity of USP Dexamethasone RS in *Mobile phase* to obtain a solution having a known concentration of about 0.12 mg per mL. Assay preparation—Dilute an accurately measured volume of

Assay preparation—Dilute an accurately measured volume of freshly mixed Ophthalmic Suspension quantitatively with *Mobile* phase to obtain a solution containing about 0.12 mg of dexamethasone per mL.

Booth per mile per mile proceed as directed for *Procedure* in the Assay for dexamethasone under Neomycin and Polymyxin B Sulfates and Dexamethasone Ophthalmic Ointment. Calculate the quantity, in mg per mL, of  $C_{22}H_{29}FO_3$  in the Ophthalmic Suspension taken by the formula:

### $(CL/D)(r_v/r_s),$

in which L is the labeled quantity, in mg per mL, of dexamethasone in the Ophthalmic Suspension, D is the concentration, in mg per mL, of dexamethasone in the Assay preparation based on the labeled quantity in the Ophthalmic Suspension and the extent of dilution, and the other terms are as defined therein.

# Neomycin and Polymyxin B Sulfates and Gramicidin Cream

» Neomycin and Polymyxin B Sulfates and Gramicidin Cream contains the equivalent of not less than 90.0 percent and not more than 130.0 percent of the labeled amounts of neomycin, polymyxin B, and gramicidin.

Packaging and storage—Preserve in collapsible tubes or in wellclosed containers.

USP Reference standards (11)—USP Gramicidin RS. USP Neomycin Sulfate RS. USP Polymyxin B Sulfate RS. Minimum fill (755): meets the requirements.

Assay for neomycin and Assay for polymyxin B—Proceed with Cream as directed in the Assay for neomycin and in the Assay for polymyxin B under Neomycin and Polymyxin B Sulfates and Bacitracin Zinc Ophthalmic Ointment.

Assay for gramicidin—Proceed with Cream as directed in the Assay for gramicidin under Neomycin Sulfate and Gramicidin Ointment.

# Neomycin and Polymyxin B Sulfates and Gramicidin Ophthalmic Solution

» Neomycin and Polymyxin B Sulfates and Gramicidin Ophthalmic Solution is a sterile, isotonic aqueous solution of Neomycin Sulfate, Polymyxin B Sulfate, and Gramicidin. It contains the equivalent of not less than 90.0 percent and not more than 130.0 percent of the labeled amounts of neomycin, polymyxin B, and gramicidin.

Packaging and storage—Preserve in tight containers. The containers or individual cartons are sealed and tamper-proof so that sterility is assured at time of first use.

**USP Reference standards** (11)—USP Gramicidin RS. USP Neomycin Sulfate RS. USP Polymyxin B Sulfate RS.

Thin-layer chromatographic identification test  $\langle 201BNP\rangle :$  meets the requirements.

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#### 1358 **Neomycin** | Official Monographs

Sterility (71)-It meets the requirements when tested as directed for Membrane Filtration under Test for Sterility of the Product to be Examined.

pH (791): between 4.7 and 6.0.

Assay for neomycin-Proceed as directed for neomycin under Antibiotics—Microbial Assays (81), using an accurately measured volume of Ophthalmic Solution diluted quantitatively and stepwise with Buffer No. 3 to yield a Test Dilution having a concentration assumed to be equal to the median dose level of the Standard.

Assay for polymyxin B-Proceed as directed for polymyxin B under Antibiotics-Microbial Assays (81), using an accurately measured volume of Ophthalmic Solution diluted quantitatively and stepwise with Buffer No. 6 to yield a Test Dilution having a concentration assumed to be equal to the median dose level of the Standard. Add to each test dilution of the Standard a quantity of USP Neomycin Sulfate RS, dissolved in Buffer No. 6, to obtain the same concentration of neomycin as is present in the Test Dilution.

Assay for gramicidin-Proceed as directed for gramicidin under Antibiotics-Microbial Assays (81), using an accurately measured volume of Ophthalmic Solution diluted quantitatively and stepwise with alcohol to yield a Test Dilution having a concentration assumed to be equal to the median dose level of the Standard.

# Neomycin and Polymyxin B Sulfates, Gramicidin, and Hydrocortisone Acetate Cream

» Neomycin and Polymyxin B Sulfates, Gramicidin, and Hydrocortisone Acetate Cream contains the equivalent of not less than 90.0 percent and not more than 130.0 percent of the labeled amounts of neomycin, polymyxin B, and gramicidin, and not less than 90.0 percent and not more than 110.0 percent of the labeled amount of hydrocortisone acetate (C23H32O6).

Packaging and storage-Preserve in well-closed containers.

USP Reference standards (11)-USP Gramicidin RS. USP Hydrocortisone Acetate RS. USP Neomycin Sulfate RS. USP Polymyxin B Sulfate RS.

Minimum fill (755): meets the requirements.

Assay for neomycin and Assay for polymyxin B-Proceed with Cream as directed in the Assay for neomycin and in the Assay for polymyxin B under Neomycin and Polymyxin B Sulfates and Bacitracin Zinc Ophthalmic Ointment.

Assay for gramicidin-Proceed with Cream as directed in the Assay for gramicidin under Neomycin Sulfate and Gramicidin Ointment. Assay for hydrocortisone acetate-Proceed with Cream as directed in the Assay under Hydrocortisone Acetate Lotion.

# Neomycin and Polymyxin B Sulfates and Hydrocortisone Otic Solution

» Neomycin and Polymyxin B Sulfates and Hydrocortisone Otic Solution is a sterile solution containing the equivalent of not less than 90.0 percent and not more than 130.0 percent of the labeled amounts of neomycin and polymyxin B. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of hydrocortisone. It may contain one or more suitable buffers. dispersants. and solvents.

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Packaging and storage-Preserve in tight, light-resistant containers The containers or individual cartons are sealed and tamper-proof as that sterility is assured at time of first use.

USP Reference standards (11)—USP Hydrocortisone RS. USP Neomycin Sulfate RS. USP Polymyxin B Sulfate RS. Sterility (71): meets the requirements.

pH (791): between 2.0 and 4.5.

Assay for neomycin—Proceed as directed under Antibiotics— Microbial Assays (81), using an accurately measured volume of Otic Solution diluted quantitatively and stepwise with Buffer No. 3 to yield a Test Dilution having a concentration assumed to be equal to the median dose level of the Standard (1.0 µg of neomycin per mL) Assay for polymyxin B-Proceed as directed under Antibiotic Microbial Assays (81), using an accurately measured volume of Of Solution diluted quantitatively and stepwise with Buffer No. 6 to yield a Test Dilution having a concentration assumed to be equal to the median dose level of the Standard (10 Polymyxin B Units per mL) Add to each test dilution of the Standard a quantity of Neomyc Standard, dissolved in Buffer No. 6, to obtain the same concentration of neomycin present in the Test Dilution.

Assay for hydrocortisone-

ssay for hydrocortisone-Mobile phase, Standard preparation, and Chromatographic directed in the Assay for hydrocortisone under system—Prepare as directed in the Assay for hydrocortisone und Neomycin and Polymyxin B Sulfates, Bacitracin Zinc and Hydro cortisone Ophthalmic Ointment.

Assay preparation-Transfer 3.0 mL of Otic Solution to a 200volumetric flask, dilute with a mixture of methanol and water (1:1) volume, and mix.

Procedure-Proceed as directed for Procedure in the Assay hydrocortisone under Neomycin and Polymyxin B Sulfates, Bacing cin Zinc and Hydrocortisone Ophthalmic Ointment, Calculate quantity, in mg, of C21H30O5 in each mL of the Otic Solution taken the formula:

#### $(66.67C)(r_v/r_s),$

in which C is the concentration, in mg per mL, of U Hydrocortisone RS in the Standard preparation, and  $r_0$  and  $r_5$ the peak responses obtained from the Assay preparation and Standard preparation, respectively.

# Neomycin and Polymyxin B Sulfates and Hydrocortisone Ophthalmic Suspension

» Neomycin and Polymyxin B Sulfates and Hydroc tisone Ophthalmic Suspension is a sterile, aques suspension containing the equivalent of not less th 90.0 percent and not more than 130.0 percent of labeled amounts of neomycin and of polymyxin B contains not less than 90.0 percent and not more the 110.0 percent of the labeled amount of hydrocortison

Packaging and storage-Preserve in tight containers. The tainers or individual cartons are sealed and tamper-proof so sterility is assured at time of first use.

USP Reference standards (11)—USP Hydrocortisone RS. Neomycin Sulfate RS. USP Polymyxin B Sulfate RS.

Thin-layer chromatographic identification test (201BNP) meets the requirements.

Sterility (71): meets the requirements.

pH (791): between 4.1 and 7.0.

Assay for neomycin-Proceed as directed for neomycin Antibiotics—Microbial Assays (81), using an accurately measured under the supersion, freshly mixed and free from bubbles, diluted quantitatively and stepwise with Buffer No. 3 tot a Test Dilution baying a concentration supersion in the source of the supersion o a Test Dilution having a concentration assumed to be equal to median dose level of the Standard.

Assay for polymyxin B-Proceed as directed for polymyxin B Antihiotics-Microbial Assays (81) using an accurately m

of Ophthalmic Suspe s, diluted quantitatively Dilution having a cor billution naving a cor in dose level of the Sta and a quantity of Neomy yield the same concent nilution.

for hydrocortisonebile phase, Standard Prepare as directed pcin and Polymyxin B ne Ophthalmic Ointm ay preparation—Trans alent to about 30 mg of dilute with a mixture ( mix. Filter the solution, ocedure—Proceed as d cortisone under Neomy finc and Hydrocortisor ity, in mg, of  $C_{21}H_3$ 20

which C is the conc ocortisone RS in the S L of Ophthalmic Susp the interact from the ses obtained from th aration, respectively.

# omycin and P drocortisone (

comycin and Poly ne Otic Suspension equivalent of not le 130.0 percent of of polymyxin B. ent and not more unt of hydrocortis ble buffers, disper

aging and storage—F crility is assured at ti Reference standard ycin Sulfate RS. USF Hayer chromatogral the requirements.

**Thy** (71): meets the **791**): between 3.0 : for neomycin and tely measured volun om air bubbles, proc he Assay for polymy. and Hydrocortison for hydrocortisone vile phase, Standa Prepare as directe cin and Polymyxin me Ophthalmic Oini by preparation-Tra mixture of methan e solution, rejectin rtisone under Neo and Hydrocortis

Slayback Exhibit 1055, Page 53 of 78 Slayback v. Eye Therapies - IPR2022-00142 1400 Norfloxacin / Official Monographs

# Norfloxacin Ophthalmic Solution

» Norfloxacin Ophthalmic Solution is a sterile, aqueous solution of Norfloxacin. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of norfloxacin (C16H18FN3O3).

Packaging and storage-Preserve in tight, light-resistant containers, stored at controlled room temperature.

USP Reference standards (11)-USP Norfloxacin RS.

Identification-

Ultraviolet Absorption (197U)-A: Solution: about 0.06 mg of norfloxacin per mL.

Diluent: 0.1 N hydrochloric acid.

B: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

Sterility (71): meets the requirements.

pH (791): between 5.0 and 5.4.

Assay— Dilute phosphoric acid solution—Prepare a solution of phosphoric

acid in water (1 in 1000). Mobile phase—Prepare a filtered and degassed mixture of Dilute phosphoric acid solution and acetonitrile (850:150). Make adjust-ments if necessary (see System Suitability under Chromatography (621)).

Standard preparation-Prepare a solution of USP Norfloxacin RS in Dilute phosphoric acid solution having a known concentration of about 0.06 mg per mL.

Resolution solution-Prepare a solution of USP Norfloxacin RS and pipemidic acid in *Dilute phosphoric acid solution* having known concentrations of about 0.06 mg of each per mL.

Assay preparation-Dilute an accurately measured volume of Ophthalmic Solution quantitatively and stepwise with Dilute phosphoric acid solution to obtain a solution having a concentration of about 0.06 mg of norfloxacin per mL. Chromatographic system (see Chromatography (621))—The liquid chromatograph is equipped with a 278-nm detector and a

3.9-mm  $\times$  30-cm column that contains packing L1. The column temperature is maintained at 50°. The flow rate is about 0.5 mL per minute. Precondition the column for about 8 hours with 0.01 M monobasic sodium phosphate buffer adjusted with phosphoric acid to a pH of 4.0. Chromatograph the *Resolution solution*, and record the peak responses as directed for *Procedure*: the relative retention times are about 0.8 for pipemidic acid and 1.0 for norfloxacin; and the resolution, R, between the pipernidic acid peak and the norfloxacin peak is not less than 1.2. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the tailing

factor for the norfloxacin peak is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%. *Procedure*—[NOTE—Use peak areas where peak responses are indicated.] Separately inject equal volumes (about 10 µL) of the Standard preparation and the Assay preparation into the chromat-ograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of norfloxacin  $(C_{16}H_{18}FN_3O_3)$  in each mL of the Ophthalmic Solution taken by the formula:

#### $(L/D)(C)(r_U/r_s),$

in which L is the labeled quantity, in mg per mL, of norfloxacin in the Ophthalmic Solution; D is the concentration, in mg per mL, of norfloxacin in the Assay preparation, based on the labeled quantity of Noncotation in the Assay preparation, value on the factor quanty of dilution; C is the concentration, in mg per mL, of USP Norfloxacin RS in the Standard preparation; and  $r_u$  and  $r_s$  are the norfloxacin peak responses obtained from the Assay preparation and the Standard preparation, respectively.

# Norfloxacin Tablets

» Norfloxacin Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of Norfloxacin (C<sub>16</sub>H<sub>18</sub>FN<sub>3</sub>O<sub>3</sub>).

Packaging and storage-Preserve in well-closed containers. USP Reference standards (11)-USP Norfloxacin RS. Identification-

Identification— A: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that of the Standard preparation obtained as directed in the Assay. B: Shake a quantity of finely powdered Tablets, equivalent to about 75 mg of norfloxacin, with 50 mL of a mixture of active unterpart (argument by mixing 1000 mL of methand and 0 mb at the standard of the st

methanol (prepared by mixing 1000 mL of methanol and 9 mL hydrochloric acid) and methylene chloride (1:1). Centrifuge hydrothorno f the suspension thus obtained, and use the clear supernation as the test solution. Apply 50  $\mu$ L each of the test solution and a standard solution of USP Norfloxacin RS in the same solver containing 1.5 mg per mL to a suitable thin-layer chromatogra plate (see Chromatography (621)) coated with a 0.25-mm layer chromatographic silica gel mixture. Place the plate in a suitab chromatographic chamber that contains and has been equilibrate with a developing system consisting of a mixture of chlorofor methanol, toluene, diethylamine, and water (40:40:20:14:8), develop the chromatogram until the solvent front has moved ab three-fourths of the length of the plate. Remove the plate from the chamber, mark the solvent front, and allow the solvent to evapor Locate the spots on the plate by examination under short-wave UV light: the  $R_F$  value of the principal spot obtained from the tensolution corresponds to that obtained from the Standard solution/ Dissolution (711)-

Dissolution (711)— pH 4.0 buffer—To 900 mL of water in a 1000-mL volumetric fla add 2.86 mL of glacial acetic acid and 1.0 mL of a 50% (wh solution of sodium hydroxide, dilute with water to volume, and we solution to a pH of 4.0. Medium: pH 4.0 buffer; 750 mL. Apparatus 2: 50 rpm. Time: 30 minutes. Procedure—Determine the amount of C. H. EN O. discolved in

*Ime:* 50 minutes. *Procedure*—Determine the amount of  $C_{16}H_{18}FN_3O_3$  dissolved in UV absorbances at the wavelength of maximum absorbance at an 278 nm of filtered portions of the solution under test, suitably dist with *Dissolution Medium*, if necessary, in comparison with Standard solution having a known concentration of USP Norflet RS in the same medium.

Tolerances—Not less than 80% (Q) of the labeled amount  $C_{16}H_{18}FN_3O_3$  is dissolved in 30 minutes.

Uniformity of dosage units (905): meet the requirements.

Mobile phase—Prepare a filtered and degassed mixture phosphoric acid solution (1 in 1000) and acetonitrile (850.1 Make adjustments if necessary (see System Suitability Chromatography (621)).

*Chromatography* (621)). *Standard preparation*—Dissolve an accurately weighed quanti USP Norfloxacin RS quantitatively in *Mobile phase*, and a quantitatively, and stepwise if necessary, with *Mobile phase* to a a solution having a known concentration of about 0.2 mg per than the phase to be a solution of about 0.2 mg per than the phase to be a solution having a known concentration of about 0.2 mg per than the phase to be a solution having a known concentration of about 0.2 mg per than the phase to be a solution having a known concentration of about 0.2 mg per than the phase to be a solution having a known concentration of about 0.2 mg per than the phase to be a solution having a known concentration of about 0.2 mg per than the phase to be a solution having a known concentration of about 0.2 mg per than the phase to be a solution having a known concentration of about 0.2 mg per than the phase to be a solution having a known concentration of about 0.2 mg per than the phase to be a solution having a known concentration of about 0.2 mg per than the phase to be a solution having a known concentration of about 0.2 mg per than the phase to be a solution having a known concentration of about 0.2 mg per than the phase to be a solution having a known concentration of about 0.2 mg per than the phase to be a solution having a known concentration of about 0.2 mg per the phase to be a solution to be a

Assay preparation—Weigh and finely powder not less that Assay preparation—weigh and finely powder not less mar Tablets. Transfer an accurately weighed portion of the port equivalent to about 100 mg of norfloxacin, to a 200-mL volum flask. Add 80 mL of Mobile phase, sonicate for 10 minutes, with phosphoric acid solution (1 in 1000) to volume, and Transfer 10.0 mL of this solution to a 25-mL volumetric flask, with Mobile phase to volume mix and filter theory the filter has with Mobile phase to volume, mix, and filter through a filter has porosity of 1 µm or less.

Chromatographic system (see Chromatography (621))-liquid chromatograph is equipped with a 275-nm detector a 3.9-mm × 30-cm column that contains packing L1, and is open 40 ± 1.0°

Precondition the column with degassed 0.01 M monobasics phosphate adjusted with phosphoric acid to a pH of 4.0, flowing rate of 0.5 mL per minute for 8 hours. For the assay, use a phase flow rate of about 2 mL per minute. Chromatograf Standard preparation, and record the peak responses as direct phosphate adjusted with phosphoric acid to a pH of 4.0, flowing

USP 28 P 28

> edure: the capacity f ciency is not less than 1 norfloxacin peak is no ation for replicate inje procedure-[NOTE-Use cated.] Separately inje and and preparation and wh, record the chroma the major peaks. Calcul portion of Tablets take:

> which C is the concentr in the Standard prepara ponses obtained from 1 paration, respectively.

# orgestimate

H<sub>31</sub>NO<sub>3</sub> 369.50 19-Dinor-17-pregn-4-en oxime, (17α)-(--13-Ethyl-17-hydroxy-1 oxime acetate (ester)

Norgestimate is a : wing a ratio of (E)-78 and it contains no ore than 102.0 percer ed basis.

#### ckaging and storage—F P Reference standards tification-

Infrared Absorption Test specimen—Use a dis specimen with mixing the specimen with The retention time o Assay preparation corres lard preparation, as ot cific rotation (781S): Test solution: 10 mg pe

on drying (731)—Dry 0.5% of its weight.

idue on ignition (281): wy metals, Method II (2 nit of residual solvents-mernal standard solution. of solution.

ndard solution-Prep tion containing 5 µL opropyl ether, and metha stem suitability solutic ming 0.05 µL each of a , and methanol per 100 solution-Transfer ab hal standard solution to and shake well to disso atographic system atograph is equipped v

# Slayback Exhibit 1055, Page 54 of 78 Slayback v. Eye Therapies - IPR2022-00142

and  $r_i$  is the total area of the peaks, except for the solvent peak: not more than 0.2% is found. Calculate the percentage of each other impurity with an area greater than that of the ofloxacin peak in the chromatogram of the System suitability standard solution obtained under Chromatographic system, by the formula:

### $100(r_i/r_i),$

in which  $r_i$  is the peak area for an individual impurity; and  $r_i$  is the total area of the peaks in the chromatogram obtained from the Test solution, except for the solvent peak: not more than 0.3% of any individual impurity is found; and the sum of all impurities found is not more than 0.5%

#### Limit of methanol and ethanol-

Internal standard solution—Prepare a solution in sodium hydrox-ide solution (1 in 100) containing  $0.7 \,\mu$ L of *n*-propyl alcohol per mL. Transfer 2.0 mL of this solution to a 250-mL volumetric flask, dilute with the same sodium hydroxide solution (1 in 100) to volume, and mix.

Standard solution—Prepare a solution in Internal standard solution containing  $10.0 \mu g$  each of methanol and dehydrated alcohol per mL. Transfer 2.0 mL of this solution to a vial fitted with a septum and crimp cap, and seal. Heat the sealed vial at 90° for 2 minutes, and shake for 6 minutes.

Test solution—Transfer 40 mg of Ofloxacin, accurately weighed, to a vial fitted with a septum and a crimp cap, add 2.0 mL of *Internal* standard solution, and seal the vial. Heat the sealed vial at 90° for 2 minutes, and shake for 6 minutes. Blank—Transfer 2.0 mL of the Internal standard solution to a vial

fitted with a septum and crimp cap, and seal. Heat the sealed vial at 90° for 2 minutes, and shake for 6 minutes.

Chromatographic system (see Chromatography  $\langle 621 \rangle$ )—The gas chromatograph is equipped with a flame-ionization detector, a 0.53-mm × 30-m fused silica column coated with a 3.0-µm film of stationary phase G43, and a fused silica precolumn. Helium is used as the carrier gas at a flow rate of about 7 mL per minute. The injection port and detector temperatures are maintained at about 170° and 250 respectively. Condition the column with the helium flowing at 200° for 2 hours or until a stable baseline is obtained. For analysis, the column temperature is programmed according to the following steps. It is maintained at  $35^{\circ}$  for 3 minutes, then increased to  $90^{\circ}$  at a rate of  $20^{\circ}$  per minute, then increased further to  $200^{\circ}$  at a rate of  $40^{\circ}$  per minute, and then maintained for 2 minutes. Chromatograph the headspace of the Standard solution, and record the peak responses as directed for *Procedure:* the relative retention times are about 0.5 for methanol, 0.6 for ethanol, and 1.0 for n-propyl alcohol; the resolution, R, between the methanol peak and the ethanol peak is not less than 2.0; and the relative standard deviation for replicate injections is not more than 5%.

Procedure—Use a heated gas tight syringe to make injections of the headspace into the chromatograph. Separately inject equal volumes (about 1 mL) of the headspace of the Standard solution, the Blank, and the Test solution into the chromatograph, record the chromatograms, and measure the peak area responses. Calculate the percentage of methanol and ethanol in the Ofloxacin taken by the formula:

#### $(2/W)(R_U - R_B)/(R_S - R_B),$

in which W is the weight, in mg, of Ofloxacin taken to prepare the *Test* solution; and  $R_U$ ,  $R_s$ , and  $R_s$  are the peak response ratios of the relevant alcohol peak to the internal standard peak obtained from the Test solution, the Blank, and the Standard solution, respectively: not more than 0.005% of methanol and not more than 0.05% of ethanol are found.

Assay-Transfer about 100 mg of Ofloxacin, accurately weighed, to a 400-mL beaker, add 275 mL of acetic anhydride, and stir to dissolve. Titrate with 0.1 N perchloric acid VS, determining the endpoint potentiometrically, using a glass-silver, distinuing the system (see *Titrimetry* (541)). Use the first of the two inflection points. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 36.138 mg of C18H20FN3O4.

# **Ofloxacin Ophthalmic Solution**

» Ofloxacin Ophthalmic Solution is a sterile aque solution of Ofloxacin. It contains not less than or percent and not more than 110.0 percent of the label amount of ofloxacin (C18H20FN3O4).

Packaging and storage-Preserve in tight containers at cont room temperature.

USP Reference standards (11)-USP Ofloxacin RS. Identification-

A: Thin-Layer Chromatographic Identification Test (201) Test solution—Dilute a portion of Ophthalmic Solution with mixture of chloroform and methanol (1:1) to obtain a solution ba a concentration of about 0.3 mg of ofloxacin per mL. Standard solution—Dissolve an accurately weighed quant

USP Ofloxacin RS in a mixture of chloroform and methanol (1) obtain a solution having a concentration of 3.0 mg per mL. The 5.0 mL of this solution to a 50-mL volumetric flask, add 5 m water, dilute with a mixture of chloroform and methanol (1: volume, and mix.

Application volume: 2 μL. Developing solvent system: a mixture of chloroform, met and a solution (1 in 30) of ammonium hydroxide (150:75 Saturate a paper-lined chromatographic chamber with this mit B: The retention time of the ofloxacin peak in the chromato

of the Assay preparation corresponds to that in the chromatog the Standard preparation, as obtained in the Assay. Sterility (71)-It meets the requirements when tested as direct

Membrane Filtration under Test for Sterility of the Product Examined.

pH (791): between 6.0 and 6.8.

Assay

Mobile phase—Prepare a filtered and degassed mixture of so dodecyl sulfate (0.24% aqueous solution), acetonitrile, and g acetic acid (580:400:20). Make adjustments if necessary

System Suitability under Chromatography (621)). 0.05N Hydrochloric acid—Add 4.0 mL of hydrochloric ac 500 mL of water, dilute with water to 1000 mL, and mix. Resolution solution—Prepare a solution of about 0.1 mg of Offoxacin RS and about 2.4 mg of propylparaben in each m

acetonitrile.

Standard preparation—Quantitatively dissolve an accu weighed quantity of USP Ofloxacin RS in 0.05 N Hydrod acid to obtain a solution having a known concentration of about mg per mL.

Assay preparation—Transfer an accurately measured volu Ophthalmic Solution, equivalent to about 3 mg of ofloxacin, w mL volumetric flask, dilute with 0.05 N Hydrochloric acid to volu and mix.

Chromatographic system (see Chromatography (621)) liquid chromatograph is equipped with a 294-nm detector 4.6-mm × 25-cm column that contains 5-µm packing L1. In rate is about 1.5 mL per minute. The column temperature maintained at a constant temperature of about 35°. Chromat the *Resolution solution*, and record the peak responses as direct Procedure: the resolution, and record the peak responses as difference in the resolution, R, between propylparaben and often not less than 2. Chromatograph the Standard preparation, and the peak responses as directed for Procedure: the tailing factor more than 3: and the relative resolution in the peak response in the p more than 3; and the relative standard deviation for reinjections is not more than 2.0%.

Procedure-Separately inject equal volumes (about 20 µL) Standard preparation and the Assay preparation into the ch ograph, record the chromatograms, and measure the areas major peaks. Calculate the quantity, in mg, of of  $(C_{18}H_{20}FN_3O_4)$  in each mL of the Ophthalmic Solution taken formula: formula:

#### $50(C/V)(r_u/r_s),$

in which C is the concentration, in mg per mL, of USP Office in the Standard preparation; V is the volume, in mL, of Op Solution taken to prepare the Assay preparation; and  $r_0$  and  $r_0$ ofloxacin peak areas obtained from the Assay preparation Standard preparation, respectively.

# rophilic O

28

USP

## enare Hydrophi

Methylparaben ropylparaben odium Lauryl S ropylene Glyco stearyl Alcohol White Petrolatun wified Water To make abou

elt the Stearyl A am bath, and dients, previo med to 75°, and

iging and storage

# hite Ointmeı

epare White Oil

White Wax . . . hite Petrolatun To make. . . .

elt the White W the White Petr intinue the hea is to congeal.

ging and storage-

# ow Ointme

pare Yellow Oi

llow Wax... trolatum To make ....

elt the Yellow add the Petro ntinue the hea s to congeal.

ging and storage-

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ies (about 20 µL) of ation into the chron sure the response for  $f C_{16}H_{24}N_2O \cdot HCl$  in en by the formula:

ng per mL, of U tion, and ru and r. iy preparation and

ide Nasal

asal Solution is chloride in wa ntains not less t 0.0 percent of

ontainers.

metazoline Hydroch

Solution, equivalent e, in a 60-mL separat nL of sodium carbo roform, and transfer separator. Extract ydrochloric acid, a r. Transfer 8 mL of y the dropwise add N sodium hydroxide itroferricyanide TS 100), mix, and allo acid dropwise until or 10 minutes: a w

Assay under Oxy

of USP Oxymetal a known concent ntration of the

-Proceed as direct each mL of the

# Oxymetazoline Hydrochloride Ophthalmic Solution

Oxymetazoline Hydrochloride Ophthalmic Solution is sterile, buffered solution of Oxymetazoline Hydrobloride in water adjusted to a suitable tonicity. It intains not less than 90.0 percent and not more than 10.0 percent of the labeled amount of C16H24N2O · HCl. contains a suitable preservative.

ckaging and storage—Preserve in tight containers. SP Reference standards (11)—USP Oxymetazoline Hydrochlo-Spic RS.

entification—A volume of Ophthalmic Solution, equivalent to aut 2.5 mg of oxymetazoline hydrochloride, responds to the ntification test under Oxymetazoline Hydrochloride Nasal Solu-

erility (71): meets the requirements.

(791): between 5.8 and 6.8.

Mobile phase-Prepare as directed in the Assay under Oxymetazne Hydrochloride.

nouncura preparation—Prepare a solution of USP Oxymetazoline indechloride RS in *Mobile phase*, having a known concentration proximately equal to the labeled concentration of the Ophthalmic variant.

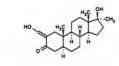
Assay preparation-Use Ophthalmic Solution.

Chromatographic system and Procedure-Proceed as directed in Assay under Oxymetazoline Hydrochloride, except to calculate quantity, in mg, of  $C_{16}H_{24}N_2O \cdot HCl$  in each mL of the Ophthalmic fution taken by the formula:

$$C(r_u/r_s),$$

which the terms are as defined therein.

### **Exymetholone**



H<sub>32</sub>O<sub>3</sub> 332.48

ostan-3-one, 17-hydroxy-2-(hydroxymethylene)-17-methyl-, (5α,17β)-.

-Hydroxy-2-(hydroxymethylene)-17-methyl-5α-androstan-3-one [434-07-1].

Dymetholone contains not less than 97.0 percent and more than 103.0 percent of C<sub>21</sub>H<sub>32</sub>O<sub>3</sub>, calculated on dried basis.

Reference standards (11)—USP Oxymetholone RS. pleteness of solution—Dissolve 100 mg in 5 mL of dioxane: the non is clear and free from undissolved solid.

tification-

Infrared Absorption (197K) Ultraviolet Absorption (197U)-

outraviolet Aosorptic. oution: 10 µg per mL. edium: 0.01 N methanolic sodium hydroxide. tic rotation (781S): between +34° and +38°. *t solution:* 20 mg per mL, in dioxane. Loss on drying (731)-Dry it in vacuum over phosphorus pentoxide for 4 hours: it loses not more than 1.0% of its weight.

Organic volatile impurities, Method V (467): meets the requirements Solvent-Use dimethyl sulfoxide.

Assav-

Standard preparation-Prepare as directed under Single-steroid Assay (511), using USP Oxymetholone RS.

Assay preparation-Weigh accurately about 20 mg of Oxymetholone, previously dried, dissolve in a sufficient quantity of a mixture of equal volumes of alcohol and chloroform to make 10.0 mL, and mix

Procedure-Proceed as directed for Procedure under Singlesteroid Assay (511), using a solvent system consisting of a mixture of benzene and alcohol (98:2), through the fourth sentence of the second paragraph under Procedure. Then centrifuge the tubes for 5 minutes, and determine the absorbances of the supernatants in 1-cm cells at the wavelength of maximum absorbance at about 315 nm, with a suitable spectrophotometer, against the blank. [NOTE—Use 0.01 N alcoholic sodium hydroxide, rather than alcohol, to elute the silica gel bands.] Calculate the quantity, in mg, of  $C_{21}H_{32}O_3$  in the portion of Oxymetholone taken by the formula:

#### $10C(A_u/A_s),$

in which C is the concentration, in mg per mL, of USP Oxymetholone RS in the Standard preparation, and  $A_U$  and  $A_z$  are the absorbances of the solutions from the Assay preparation and the Standard preparation, respectively.

# **Oxymetholone Tablets**

» Oxymetholone Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of C21H32O3.

# Packaging and storage-Preserve in well-closed containers.

USP Reference standards (11)-USP Oxymetholone RS. Identification—Mix an amount of powdered Tablets, equivalent to about 50 mg of oxymetholone, with 15 mL of solvent hexane, and stir occasionally for 15 minutes. Centrifuge the mixture, and decant and discard the solvent hexane. Extract the residue with two 10-mL portions of solvent hexane, centrifuging and decanting as before, and discard the solvent hexane. Add 25 mL of chloroform to the residue, mix by shaking for 1 to 2 minutes, and filter. Evaporate the filtrate to about 3 mL, add a few mL of solvent hexane to induce crystallization, and evaporate to dryness: the IR absorption spectrum of a potassium bromide dispersion prepared from the oxymetholone so obtained, and previously dried, exhibits maxima only at the same wavelengths as that of a similar preparation of USP Oxymetholone RS, crystallized from the same solvent mixture.

## Dissolution (711)

Medium: 0.05 M pH 8.5 alkaline borate buffer (see under Solutions in the section Reagents, Indicators, and Solutions); 900 mL

Apparatus 1: 100 rpm.

Time: 45 minutes.

Procedure-Determine the amount of C21H32O3 dissolved from UV absorbances at the wavelength of maximum absorbance at about 313 nm of filtered portions of the solution under test, suitably diluted with Dissolution Medium if necessary, in comparison with a Standard solution having a known concentration of USP Oxymetholone RS in the same medium. [NOTE—An amount of acetonitrile not to exceed 5% of the total volume of the Standard solution may be used to bring the Reference Standard into solution prior to dilution with Dissolution Medium.]

Tolerances-Not less than 75% (Q) of the labeled amount of C21H32O3 is dissolved in 45 minutes.

Uniformity of dosage units (905): meet the requirements.

Procedure for content uniformity-Transfer 1 finely powdered Tablet to a 100-mL volumetric flask with the aid of about 75 mL of methanol. Heat the methanol to boiling, and allow to remain at a temperature just below the boiling point for 15 minutes with

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#### 1542 **Phenylephrine** | Official Monographs

Standard preparation-Dissolve about 50 mg of USP Phenylephrine Hydrochloride RS, accurately weighed, in 10 mL of water, dilute with *Dilution solvent* to 25.0 mL, and mix. Further dilute 5.0 mL of the resulting solution with Dilution solvent to 25.0 mL, and mix to obtain a solution having a known concentration of about 0.4 mg per mL.

Assay preparation—Transfer an accurately measured volume of Injection, equivalent to about 10 mg of phenylephrine hydrochloride, to a 25-mL volumetric flask. Dilute with *Dilution solvent* to volume, and mix.

Chromatographic system (see Chromatography (621))liquid chromatograph is equipped with a 280-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is about 1 mL per minute. Chromatograph the System suitability solution, and record the responses for the major peaks: the resolution, R, between epinephrine and phenylephrine is not less than 1.0. Chromatograph replicate injections of the Standard preparation, and record the peak responses as directed for Procedure: the relative standard deviation is not more than 2.0%.

Procedure-Separately inject equal volumes (about 20 µL) of the Standard preparation and the Assay preparation into the chromat-ograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of  $C_9H_{13}NO_2 \cdot HCl$  in each mL of the Injection taken by the formula:

#### $(25C/V)(r_u/r_s),$

in which C is the concentration, in mg per mL, of USP Phenylephrine Hydrochloride RS in the *Standard preparation*, V is the volume, in mL, of Injection taken, and  $r_v$  and  $r_s$  are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.

# Phenylephrine Hydrochloride Nasal Jelly

» Phenylephrine Hydrochloride Nasal Jelly contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of C9H13NO2 · HCl.

### Packaging and storage-Preserve in tight containers.

USP Reference standards (11)-USP Phenylephrine Hydrochloride RS.

Identification—Dissolve a suitable quantity in water to obtain a solution having a concentration of about 60  $\mu$ g per mL, and solution in the solution is a contract of the solution is a control of the solution is a control of the solution is a control of the solution is obtained exhibits maxima and minima at the same wavelengths as that of a similar solution of USP Phenylephrine Hydrochloride RS, concomitantly measured.

Minimum fill (755): meets the requirements.

#### Assay

Mobile phase-Prepare a mixture of methanol and water (1:1) containing 1.1 g of sodium 1-octanesulfonate per liter, adjust with phosphoric acid to a pH of 3.0, filter, and degas. Make adjustments to the methanol and water ratio, if necessary (see System Suitability under Chromatography (621)). Dilution solvent—Prepare a mixture of methanol and water (1:1),

and adjust with phosphoric acid to a pH of 3.0.

Standard preparation --- Dissolve an accurately weighed quantity of USP Phenylephrine Hydrochloride RS in Dilution solvent to obtain a Stock standard solution having a known concentration of about 2 mg per mL. Dilute an accurately measured volume of this solution with *Dilution solvent* to obtain the *Standard preparation* having a known concentration of about 0.1 mg per mL.

Assay preparation—Transfer an accurately weighed amount of Nasal Jelly, equivalent to about 10 mg of phenylephrine hydrochloride, to a 100-mL volumetric flask. Dilute with Dilution solvent to volume, and mix.

Resolution solution-Transfer 5.0 mL of Stock standard solution to a 100-mL volumetric flask, add 10 mg of USP Epinephrine Bitartrate RS, dilute with Dilution solvent to volume, and mix.

Chromatographic system (see Chromatography (621))-The liquid chromatograph is equipped with a 280-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is about 1 mL per minute. Chromatograph the Resolution solution: in resolution, R, is not less than 1.5, and the tailing factor for the solution R is not less than 1.5, and the tailing factor for the solution. phenylephrine peak is not more than 2.0. Chromatograph replica injections of the Standard preparation: the relative standard deviation is not more than 2.0%.

Procedure-Separately inject equal volumes (about 20 µL) of Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of  $C_9H_{13}NO_2 \cdot HCI$  in the portion of Nasal Jelly taken by the formula:

### $100C(r_{U}/r_{s}),$

in which C is the concentration, in mg per mL, of USP Phenylephin Hydrochloride RS in the Standard preparation, and  $r_{ij}$  are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.

# Phenylephrine Hydrochloride Nasal Solution

» Phenylephrine Hydrochloride Nasal Solution contai not less than 90.0 percent and not more than 115 percent of the labeled amount of  $C_9H_{13}NO_2 \cdot HCl$ .

Packaging and storage-Preserve in tight, light-resistant cont USP Reference standards (11)-USP Phenylephrine Hydrock ride RS

Identification-It responds to the Identification test under Phe ephrine Hydrochloride Injection. Assay

Mobile phase, Dilution solvent, Standard preparation, Resolution solution, and Chromatographic system-Prepare as directed in

Assay under Phenylephrine Hydrochloride Nasal Jelly. Assay preparation—Transfer an accurately measured volume Nasal Solution, equivalent to about 10 mg of phenyleph hydrochloride, to a 100-mL volumetric flask. Dilute with Ding solvent to volume, and mix.

Procedure-Separately inject equal volumes (about 20 µL) of Standard preparation and the Assay preparation into the chronograph, record the chromatograms, and measure the responses for major peaks. Calculate the quantity, in mg, of  $C_9H_{13}NO_2 \cdot HCl$  in mL of the Nasal Solution taken by the formula:

#### $100(C/V)(r_u/r_s),$

in which C is the concentration, in mg per mL, of USP Phenyleph Hydrochloride RS in the Standard preparation, V is the volume mL, of Nasal Solution taken, and  $r_U$  and  $r_s$  are the peak response obtained from the Assay preparation and the Standard prepara respectively.

# Phenylephrine Hydrochloride **Ophthalmic Solution**

» Phenylephrine Hydrochloride Ophthalmic Soluti a sterile, aqueous solution of Phenylephrine Hydrog ride. It contains not less than 90.0 percent and not than 115.0 percent of the labeled amoun  $C_9H_{13}NO_2$  HCl. It may contain a suitable antimication of the statement of the agent and buffer and may contain suitable antioxid

Packaging and storage-Preserve in tight, light-resistant con of not more than 15-mL size. USP Reference standards (11)-USP Phenylephrine Hyd ride RS.

SP 28

USP 28

tification-It resp wine Hydrochloride ility (71): meets (791): between 4 ween 3.0 and 4.5 fo

Mobile phase, Diluti Mobile phase, Diluti Jution, and Chromata say under Phenyleph Assay preparation— http:// filteration is the second se went to volume, and Procedure-Separate dard preparation a raph, record the chror r peaks. Calculate t L of Ophthalmic Solu

which C is the concer which loride RS in the of Ophthalmic Sc ponses obtained from aration, respectivel

# henylethyl Al

H10O 122.17 reneethanol nethyl alcohol 161

store in a cool, dry j tification-Transfer y isocyanate (Cau er), and heat on a st ry, and induce cr with a glass rod. Aft tion into a warm, dry s and wash them y nyl carbanilate so ing Range or Tempe fic gravity (841): ctive index (831):

the on ignition (28 ite to constant we inated compound gauze around the minous flame of a B ame green. Permit th d coat of oxide has of Phenylethyl Alc Im freely in the air. hethyl Alcohol, and f6 drops has been a er edge of the But transient green cu de-Shake 5 mL stand for 1 hour:

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. Chromatograph replice n: the relative stands

umes (about 20  $\mu$ L) of paration into the chrome assure the responses for  $z_2$ , of  $C_9H_{13}NO_2 \cdot HCl$  in that lat

mL, of USP Phenylephi ation, and  $r_{U}$  and  $r_{s}$  are say preparation and

# oride Nasal

asal Solution conta not more than 113 C<sub>9</sub>H<sub>13</sub>NO<sub>2</sub> · HCl.

it, light-resistant contai Phenylephrine Hydroe

fication test under Phen

urd preparation, Resolution -Prepare as directed in le Nasal Jelly. ately measured volume, 10 mg of phenylephi flask. Dilute with Dilut

lumes (about 20 µL) of paration into the chr easure the responses for ;, of C<sub>9</sub>H<sub>13</sub>NO<sub>2</sub> · HCl in mula:

,),

mL, of USP Phenyleph aration, V is the volume  $1 r_s$  are the peak response 1 the Standard preparation

### oride

**Dphthalmic Solution** nylephrine Hydroch ) percent and not m labeled amount i suitable antimicro 1 suitable antioxida

ht, light-resistant conta

Phenylephrine Hydro

ptification-It responds to the Identification test under Phenylrine Hydrochloride Injection. hity (71): meets the requirements.

(791): between 4.0 and 7.5 for buffered Ophthalmic Solution; ween 3.0 and 4.5 for unbuffered Ophthalmic Solution.

Mobile phase, Dilution solvent, Standard preparation, Resolution Mobile phase, Dilution solvent, Standard preparation, Resolution and Chromatographic system—Prepare as directed in the sy under Phenylephrine Hydrochloride Nasal Jelly. Assay preparation—Transfer an accurately measured volume of hummic Solution, equivalent to about 10 mg of phenylephrine hummic to a 100 mg unput and the Dilution with Director

trochloride, to a 100-mL volumetric flask. Dilute with Dilution hent to volume, and mix.

when to volume, and thus, procedure—Separately inject equal volumes (about 20  $\mu$ L) of the indard preparation and the Assay preparation into the chromat-reph, record the chromatograms, and measure the responses for the for peaks. Calculate the quantity, in mg, of C<sub>9</sub>H<sub>13</sub>NO<sub>2</sub> · HCl in each t of Ophthalmic Solution taken by the formula:

 $100(C/V)(r_U/r_s),$ 

which C is the concentration, in mg per mL, of USP Phenylephrine trochloride RS in the Standard preparation, V is the volume, in , of Ophthalmic Solution taken, and  $r_{v}$  and  $r_{s}$  are the peak ponses obtained from the Assay preparation and the Standard paration, respectively.

# henvlethyl Alcohol



H<sub>10</sub>O 122.17

kaging and storage-Preserve in tight, light-resistant containers, store in a cool, dry place.

**utification**—Transfer 1 mL to a dry test tube, add 500  $\mu$ L of myl isocyanate (*Caution—Phenyl isocyanate is a strong lacri-*my), and heat on a steam bath for 5 minutes. Cool, using ice if essary, and induce crystallization by scratching the walls of the with a glass rod. After crystals have formed, add about 10 mL of real hexane, heat to boiling for a few minutes, and filter the minimum a warm, dry test tube. Collect the crystals that form on a and wash them with cool solvent hexane: the crystals of methyl carbanilate so obtained melt between 78° and 80° (see thing Range or Temperature (741)).

tific gravity  $\langle 841 \rangle$ : between 1.017 and 1.020.

active index (831): between 1.531 and 1.534 at 20°.

due on ignition (281)-Evaporate 10 mL in a suitable crucible, ignite to constant weight: the limit is 0.005%.

rinated compounds-Wind a 1.5- × 5-cm strip of 20-mesh gauze around the end of a copper wire. Heat the gauze in the The provided a series of the s unous flame of a Bunsen burner until it glows without coloring Methyl Alcohol, and burn as before. Community process and the process of the proc ter edge of the Bunsen flame, adjusted to a height of about 4 no transient green color or other color is imparted to the flame.

de-Shake 5 mL with 5 mL of 1 N sodium hydroxide, and to stand for 1 hour: no yellow color appears in the organic (top)

Organic volatile impurities, Method IV (467): meets the requirements.

# **Phenylpropanolamine Bitartrate**

 $C_9H_{13}NO \cdot C_2H_6O_6$  301.30 ( $R^*,S^*$ )-( $\pm$ )- $\alpha$ -(1-Aminoethyl)benzenemethanol bitartrate [67244-90-0].

» Phenylpropanolamine Bitartrate contains not less than 98.0 percent and not more than 101.0 percent of  $C_9H_{13}NO \cdot C_4H_6O_6$ , calculated on the dried basis.

Packaging and storage-Preserve in tight, light-resistant containers. USP Reference standards (11)—USP Cathinone Hydrochloride RS. USP Dextroamphetamine Sulfate RS. USP Phenylpropanediol RS. USP Phenylpropanolamine Bitartrate RS. USP Phenylpropanolamine Hydrochloride RS.

## Identification-

A: Infrared Absorption (197K).

B: It responds to the test for Tartrate (191).

Melting range, Class I (741): between 150° and 164°.

pH (791): between 3.1 and 3.7, in a solution (3 in 100).

Loss on drying (731)—Dry it at 65° for 3 hours: it loses not more than 1.0% of its weight.

Residue on ignition (281): not more than 0.1%.

Heavy metals, Method I (231)-Dissolve 1 g in 5 mL of water, add 1 mL of 1 N acetic acid, and dilute with water to 25 mL: the limit is 0.002%

Limit of cathinone hydrochloride-Proceed as directed for Limit of cathinone hydrochloride under Phenylpropanolamine Hydrochloride.

Limit of amphetamine hydrochloride and phenylpropanediol-Mobile phase-Prepare a mixture of 20 mL of 10% tetramethyl-ammonium hydroxide and 5 mL of phosphoric acid, dilute with water to a volume of 1000 mL, and mix. To 896 mL of the resulting solution add 100 mL of methanol, 4 mL of tetrahydrofuran, and mix. Filter and degas the mixture. Make adjustments if necessary (see System Suitability under Chromatography (621)). Standard solution A—Dissolve accurately weighed quantities of USP Phenylpropanolamine Hydrochloride RS and USP Dextroam-

phetamine Sulfate RS in water to obtain a solution having known concentrations of about 100 mg of USP Phenylpropanolamine Hydrochloride RS per mL and 1  $\mu$ g of USP Dextroamphetamine

Sulfate RS per mL. Standard solution B-Dissolve an accurately weighed quantity of USP Phenylpropanediol RS in water, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about 0.1 mg per mL.

Resolution solution—Dissolve accurately weighed quantities of USP Phenylpropanolamine Hydrochloride RS and USP Dextroamphetamine Sulfate RS in water to obtain a solution containing about 5 µg of each per mL

Test solution-Transfer about 1000 mg of Phenylpropanolamine Bitartrate, accurately weighed, to a 10-mL volumetric flask, dilute with water to volume, and mix.

Chromatographic system (see Chromatography (621))—The liquid chromatograph is equipped with a 215-nm detector and a 4.6-mm × 15-cm column that contains spherical 5-µm packing L1. The flow rate is about 2.0 mL per minute. Separately chromatograph the Resolution solution and each Standard solution, and record the peak responses as directed for *Procedure*: the relative retention times are about 1.0 for phenylpropanolamine, between 1.9 and 2.1 for dextroamphetamine, and between 2.3 and 2.7 for phenylpropanediol; the resolution, R, between phenylpropanolamine and dextroamphetamine in the chromatogram of the Resolution solution is not less than 5.0; and the relative standard deviation for replicate injections of the Standard solutions is not more than 3.0%.

Procedure-Separately inject equal volumes (about 20 µL) of Standard solution A, Standard solution B, and the Test solution into the chromatograph, record the chromatograms, and measure the

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interesting and a second secon [60-12-8].

USP Reference standards (11)-USP Physostigmine Salicylate RS. USP Endotoxin RS. Identification-

It responds to the Identification test under Physostigmine.

A: It responds to the *laenupcanon* is a set of the set Bacterial endotoxins (85)—It contains not more than 83.4 USP Endotoxin Units per mg of physostigmine salicylate.

pH (791): between 3.5 and 5.0.

Other requirements-It meets the requirements under Injections (1).

#### Assay

0.05 M Ammonium acetate—Dissolve 3.85 g of ammonium acetate in 1 liter of water, and adjust, if necessary, with glacial acetic acid or ammonium hydroxide to a pH of  $6 \pm 0.1$ .

Mobile phase-Prepare a filtered and degassed mixture of equal volumes of acetonitrile and 0.05 M Ammonium acetate. Make adjustments if necessary (see System Suitability under Chromatography (621))

Benzyl alcohol-benzaldehyde solution-Prepare a mixture of 100 µL of benzyl alcohol and 1 µL of benzaldehyde in each 400 mL of acetonitrile.

Standard preparation-Dissolve an accurately weighed quantity of USP Physostigmine Salicylate RS in Benzyl alcohol-benzaldehyde solution, and dilute quantitatively, and stepwise if necessary, with Benzyl alcohol-benzaldehyde solution, to obtain a solution having a known concentration of about 30 µg per mL. Assay preparation—Transfer an accurately measured volume of

Injection, equivalent to about 3 mg of physostigmine salicylate, to a 100-mL volumetric flask, dilute with acetonitrile to volume, and mix.

Chromatographic system (see Chromatography (621))—The liquid chromatograph is equipped with a 254-nm detector and a 3.9-mm  $\times$  30-cm column that contains packing L1. The flow rate is about 2 mL per minute. Separately chromatograph 10-µL portions of the Benzyl alcohol-benzaldehyde solution and the Standard prepathe Benzyl alcohol-benzalaehyde solution and the Standard prepa-ration, and record the peak responses as directed under Procedure [NOTE—If the components of the Benzyl alcohol-benzaldehyde solution co-elute, the Standard preparation will exhibit only 2 peaks instead of 3.]: in a suitable system, benzyl alcohol and benzaldehyde elute before physostigmine, the column efficiency determined from the analyte peak is not less than 1200 theoretical plates the resolution. B between physostigmine and the adjacent plates, the resolution, R, between physostigmine and the adjacent peak (benzyl alcohol or benzaldehyde or the combination of these) is not less than 2.0, and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure-Separately inject equal volumes (about 10 µL) of the Standard preparation and the Assay preparation into the chromat-ograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of C15H21N3O2 · C7H6O3 in each mL of the Injection taken by the formula:

#### $0.1(C/V)(r_v/r_s),$

in which C is the concentration, in  $\mu g$  per mL, of USP Physostigmine Salicylate RS in the Standard preparation, V is the volume, in mL, of Since the number of the second secon

# **Physostigmine Salicylate Ophthalmic** Solution

» Physostigmine Salicylate Ophthalmic Solution is a sterile, aqueous solution of Physostigmine Salicylate. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of C<sub>15</sub>H<sub>21</sub>N<sub>3</sub>O<sub>2</sub>. C7H6O3. It may contain suitable antimicrobial agents, buffers, and stabilizers, and suitable additives to increase its viscosity.

Packaging and storage-Preserve in tight, light-resistant containers, USP Reference standards (11)-USP Physostigmine Salicylate RS. Identification-It responds to the Identification tests under Physo stigmine Salicylate.

Sterility (71): meets the requirements.

pH (791): between 2.0 and 4.0.

Assav

0.05 M Ammonium acetate and Mobile phase-Prepare as directed in the Assay under Physostigmine Salicylate Injection

Standard preparation-Dissolve an accurately weighed quantity of USP Physostigmine Salicylate RS in acetonitrile, and dilute quantitatively, and stepwise if necessary, with acetonitrile, to obtain

dualitatively, and schware in concentration of about 30 µg per mL. Assay preparation—Transfer an accurately measured volume of Ophthalmic Solution, equivalent to about 3 mg of physostigmine salicylate, to a 100-mL volumetric flask, dilute with acetonitrile in volume, and mix.

Chromatographic system (see Chromatography (621))—The liquid chromatograph is equipped with a 254-nm detector and a 3.9-mm × 30-cm column that contains packing L1. The flow rate is about 2 mL per minute. Chromatograph the Standard preparation and record the peak responses as directed for Procedure: the column efficiency determined from the analyte peak is not less than 1200 theoretical plates, and the relative standard deviation for replicant injections is not more than 2.0%.

Procedure-Proceed as directed for Procedure in the Assay under Physostigmine Salicylate Injection. Calculate the quantity, in mg,  $\mathbf{a} \in C_{15}H_{21}N_3O_2 \cdot C_7H_6O_3$  in each mL of the Ophthalmic Solution taken by the formula:

#### $0.1(C/V)(r_u/r_s),$

in which the terms are as defined therein.

# **Physostigmine Sulfate**

(C<sub>15</sub>H<sub>21</sub>N<sub>3</sub>O<sub>2</sub>)<sub>2</sub>·H<sub>2</sub>SO<sub>4</sub> 648.77 Pyrrolo[2,3-b]indol-5-ol, 1,2,3,3a,8,8a-hexahydro-1,3a,8-trimethylmethylcarbamate (ester), (3aS-cis)-, sulfate (2:1). Physostigmine sulfate (2:1) [64-47-1].

» Physostigmine Sulfate contains not less than 97. percent and not more than 102.0 percent of (C15H21N3O2)2 · H2SO4, calculated on the dried basis.

Packaging and storage-Preserve in tight, light-resistant contain USP Reference standards (11)-USP Physostigmine Salicylate R Identification-

It responds to the Identification test under Physostigmine A solution (1 in 100) responds to the tests for Sulfate (199 B:

Specific rotation (781S): between -116° and -120°.

Test solution: 10 mg per mL, in water. Loss on drying (731)—Dry it at 105° to constant weight: it loses more than 1.0% of its weight.

Residue on ignition (281): negligible, from 100 mg.

Readily carbonizable substances-It meets the requirements of test for Readily carbonizable substances under Physostigmine. Assay-Dissolve about 200 mg of Physostigmine Sulfate, accum weighed, in 25 mL of water. Render the solution alkaline by addition of about 1 g of sodium bicarbonate, and extract with on mL and five 10-mL portions of chloroform, each time shall vigorously for 1 minute. Filter each extract through glass wool 15 mL of glacial acetic acid and 10 mL of acetic acid anhydride of combined chloroform extracts, and titrate with 0.02 N perchloric VS, determining the endpoint potentiometrically. Perform a v.s. uctermining the endpoint potentiometrically. Perform a c determination, and make any necessary correction. Each multiple 0.02 N perchloric acid is equivalent to 6.488 m  $(C_{15}H_{21}N_3O_2)_2 \cdot H_2SO_4$ .

USP 28

# **Physostigmine** Ointment

Physostigmine Su not less than 90.0 percent of the labele it is sterile.

#### Packaging and storage nt tubes

USP Reference standard Identification-

A: Place about 20 g bout 25 mL of water, intinuous stirring, unti congeal the ointment base iter into a separator. L Mentification test B: t. equirements of the tes Bases (181), USP Physos odium bicarbonate bein hydroxide specified. B: A 2-mL portior dentification test A respo

Sterility (71): meets th Metal particles—It mee Particles in Ophthalmic ( Assav-

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0.05 M Ammonium ace the Assay under Physo Standard preparation-SP Physostigmine Se antitatively, and stepw solution having a know Assay preparation-Ti phthalmic Ointment, ecultate, to a 60-mL sepa ade n-hexane, and extra ollect the acetonitrile ex th acetonitrile to volum Chromatographic syste directed for Chrom. sostigmine Salicylate Procedure-Proceed as hysostigmine Salicylate  $H_{21}N_3O_2)_2$   $H_2SO_4$  in on by the formula:

## (648.77

which 648.77 and vsostigmine sulfate and e concentration, in µg in the Standard prepa

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