

HOGAN & HARTSON

L.L.P.

DAVID M. FOX
PARTNER
(202) 637-5678
DMFOX@HHLAW.COM

COLUMBIA SQUARE
555 THIRTEENTH STREET, NW
WASHINGTON, DC 20004-1109
TEL (202) 637-5600
FAX (202) 637-5910
WWW.HHLAW.COM

May 5, 2005

BY HAND DELIVERY

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

**Re: Docket Nos. 2004P-0290 & 2004P-0488
Supplement to Citizen Petitions**

Dear Sir or Madam:

On behalf of GlaxoSmithKline, please submit the attached proposed United States Pharmacopeia (USP) monographs to the above-referenced citizen petitions, filed by the Food and Drug Administration on July 8 and November 5, 2004. These monographs were published in Vol. 31(2) [Mar. – Apr. 2005] of the *Pharmacopeial Forum* and currently are targeted for official adoption in the 29th revision of the USP (January 2006).

Sincerely,



David M. Fox
Brian R. McCormick
Hogan & Hartson L.L.P.

cc: David M. Cocchetto, Ph.D.
Vice President
Antiviral/Antibacterial Regulatory Affairs
GlaxoSmithKline

2004P-0290

SUP3

BERLIN BRUSSELS LONDON PARIS BUDAPEST PRAGUE WARSAW MOSCOW TOKYO

NEW YORK BALTIMORE McLEAN MIAMI DENVER BOULDER COLORADO SPRINGS LOS ANGELES
\\DC-59524/0034-2118888 v1

peak responses. Calculate the quantity, in mg, of methscopolamine bromide ($C_{18}H_{24}BrNO_4$) in the portion of Tablets taken by the formula:

$$100C(r_o/r_s),$$

in which C is the concentration, in mg per mL, of USP Methscopolamine Bromide RS in the *Standard preparation*; and r_o and r_s are the peak responses of the methscopolamine bromide obtained from the *Assay preparation* and the *Standard preparation*, respectively. \blacktriangle USP29

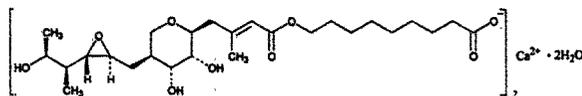
BRIEFING

Mupirocin Calcium; Mupirocin Cream. Because there are no existing *USP* monographs for this active antibiotic drug substance and dosage form, new monographs are being proposed. The liquid chromatographic procedures in the test for *Related compounds* and in the *Assay* are based on analyses performed with the Zorbax C8 brand of L7 column. In the test for *Related compounds*, typical retention times for pseudomonic acid D and mupirocin are about 9 minutes and 12 minutes, respectively. In the *Assay*, typical retention times for pseudomonic acid D and mupirocin are 7 minutes and 9 minutes, respectively.

(PA7: L. Callahan) RTS—37476-1; 41278-1

Add the following:

\blacktriangle Mupirocin Calcium



$C_{52}H_{86}CaO_{18} \cdot 2H_2O$ 1075.34

Nonanoic acid, 9-[[[3-Methyl-1-oxo-4-[tetrahydro-3,4-dihydroxy-5-[[[3-(2-hydroxy-1-methylpropyl)oxiranyl]methyl]-2H-pyran-2-yl]-2-butenyl]oxy-, calcium salt (2 : 1), dihydrate, [2*S*-[2*α*(*E*),3*β*,4*β*,5*α*[2*R**,3*R**(1*R**,2*R**)]]]]].

(*αE*,2*S*,3*R*,4*R*,5*S*)-5-[(2*S*,3*S*,4*S*,5*S*)-2,3-Epoxy-5-hydroxy-4-methylhexyl]tetrahydro-3,4-dihydroxy- β -methyl-2H-pyran-2-crotonic acid, ester with 9-hydroxynonanoic acid, calcium salt (2 : 1), dihydrate [115074-43-6].

» Mupirocin Calcium contains the equivalent of not less than 865 μ g and not more than 936 μ g of mupirocin ($C_{26}H_{44}O_9$) per mg.

Packaging and storage—Preserve in tight containers. Store at 25°, excursions permitted between 15° and 30°.

USP Reference standards (11)—*USP Mupirocin Calcium RS*. *USP Mupirocin Lithium RS*.

Identification

A: *Infrared Absorption* (197M)—[NOTE—Do not heat or grind extensively.]

B: *Ultraviolet Absorption* (197U)—

Solution: 20 μ g per mL.

Medium: methanol.

C: When moistened with hydrochloric acid, it meets requirements of the flame test for *Calcium* (191).

Crystallinity (695): meets the requirement.

Specific rotation (781S): between -16° and -20° .

Test solution: 50 mg per mL, in methanol.

Water, Method I (921): not less than 3.0% and not more than 4.5%.

Chloride (221)—Dissolve 50 mg in a mixture of 1 mL of 2 N nitric acid and 15 mL of methanol. Add 1 mL of silver nitrate TS: the turbidity does not exceed that produced by 0.70 mL of 0.020 N hydrochloric acid (0.5%).

Related compounds—

0.1 M Ammonium acetate—Prepare as directed in the *Assay*.

Mobile phase—Prepare a filtered and degassed mixture of 0.1 M Ammonium acetate and tetrahydrofuran (70 : 30). Make adjustments if necessary (see *System Suitability* under *Chromatography* (621)).

pH 4 Acetate buffer—Transfer about 13.6 g of sodium acetate to a 1000-mL volumetric flask, and dissolve in about 900 mL of water. Adjust with glacial acetic acid to a pH of 4.0, and dilute with water to volume.

Diluent—Prepare a mixture of *pH 4 Acetate buffer* and methanol (1 : 1).

Standard solution—Transfer about 25 mg of USP Mupirocin Lithium RS, accurately weighed, to a 200-mL volumetric flask, dissolve in and dilute with *Diluent* to volume, and mix.

Test solution—Transfer about 50 mg of Mupirocin Calcium, accurately weighed, to a 10-mL volumetric flask, dissolve in and dilute with *Diluent* to volume, and mix.

Resolution solution—Adjust 10 mL of the *Standard solution* with 6 N hydrochloric acid to a pH of 2.0, allow to stand for 20 hours, and adjust with 5 N sodium hydroxide to a pH of 4.0.

Chromatographic system (see *Chromatography* (621))—The liquid chromatograph is equipped with a 240-nm detector and a 4.6-mm × 25-cm column that contains 7- μ m packing L7. The flow rate is about 1 mL per minute. Chromatograph the *Resolution solution*, and record the peak responses as directed for *Procedure*: the resolution, *R*, between the second of two peaks corresponding to hydroly-

ysis products and the peak corresponding to mupirocin is not less than 7.0. Chromatograph the *Standard solution*, and record the peak responses as directed for *Procedure*: the relative retention times are about 0.75 (6 minutes) for pseudomonic acid D and 1.0 (14 minutes) for mupirocin; the column efficiency for the mupirocin peak is not less than 3000 theoretical plates; the tailing factor for the mupirocin peak is not more than 2; and the relative standard deviation of the mupirocin peak for replicate injections is not more than 5%.

Procedure—Separately inject equal volumes (about 20 μ L) of the *Standard solution* and the *Test solution* into the chromatograph, and measure the peak area responses for all of the peaks. Calculate the percentage of each related compound in the portion of Mupirocin Calcium taken by the formula:

$$(E/200)(W_s/W_o)(r_i/r_s),$$

in which *E* is the mupirocin equivalent, in μ g per mg, of USP Mupirocin Lithium RS; *W_s* is the weight, in mg, of USP Mupirocin Lithium RS taken to prepare the *Standard solution*; *W_o* is the weight, in mg, of Mupirocin Calcium taken to prepare the *Test solution*; *r_i* is the peak area for any impurity obtained from the *Test solution*; and *r_s* is the peak area for mupirocin obtained from the *Standard solution*: the area of any peak corresponding to pseudomonic acid D is not greater than 2.5%; the area of any peak, excluding the mupirocin peak and any peak corresponding to pseudomonic acid D, is not greater than 1%; and the sum of the areas of all the peaks, excluding the principal peak, is not greater than 4.5%. Disregard any peak with an area less than 0.05 times the area of the mupirocin peak in the chromatogram obtained from the *Standard solution*.

Assay—

0.1 M Ammonium acetate—Transfer about 7.7 g of ammonium acetate to a 1000-mL volumetric flask, dissolve in about 900 mL of water, adjust with glacial acetic acid to a pH of 5.7, and dilute with water to volume.

Mobile phase—Prepare a filtered and degassed mixture of *0.1 M Ammonium acetate* and tetrahydrofuran (68 : 32). Make adjustments if necessary (see *System Suitability* under *Chromatography* (621)).

Standard preparation—Transfer about 25 mg of USP Mupirocin Lithium RS, accurately weighed, to a 200-mL volumetric flask, dissolve in 5 mL of methanol, dilute with *0.1 M Ammonium acetate* to volume, and mix.

Assay preparation—Transfer about 25 mg of Mupirocin Calcium, accurately weighed, to a 200-mL volumetric flask, dissolve in 5 mL of methanol, dilute with *0.1 M Ammonium acetate* to volume, and mix.

Resolution solution—Adjust 10 mL of the *Standard preparation* with 6 N hydrochloric acid to a pH of 2.0, and allow to stand for 20 hours.

Chromatographic system (see *Chromatography* (621))—The liquid chromatograph is equipped with a 230-nm detector and a 4.6-mm × 25-cm column that contains 7-μm packing L7. The flow rate is about 1 mL per minute. Chromatograph the *Resolution solution*, and record the peak responses as directed for *Procedure*: the resolution, *R*, of the second of the two peaks corresponding to hydrolysis products and the peak corresponding to mupirocin is not less than 7.0. Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure*: the relative standard deviation for replicate injections is not more than 1.0%.

Procedure—Separately inject equal volumes (about 20 μL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, and measure the peak area respon-

ses for the major peaks. Calculate the quantity, in μg, of mupirocin (C₂₆H₄₄O₉) in each mg of Mupirocin Calcium taken by the formula:

$$E(M_s/M_u)(r_u/r_s),$$

in which *E* is the designated mupirocin equivalent, in μg, of mupirocin in each mg of the USP Mupirocin Lithium RS. *M_s* is the weight, in mg, of USP Mupirocin Lithium RS taken to prepare the *Standard preparation*; *M_u* is the weight, in mg, of Mupirocin Calcium taken to prepare the *Assay preparation*; and *r_u* and *r_s* are the mupirocin peak area responses obtained from the *Assay preparation* and the *Standard preparation*, respectively. ▲*USP29*

BRIEFING

Mupirocin Cream—See briefing under *Mupirocin Calcium*. In the test for *Related compounds*, typical retention times are about 7.6 minutes for pseudomonic acid F; 12.8 and 13.6 minutes for degradation products; 15.8 and 19.4 minutes for pseudomonic acid D and pseudomonic acid B, respectively; 21.5 minutes for mupirocin; 24.7 and 26.5 minutes for other impurities; and 43.6 and 50.1 minutes for pseudomonic acid C and pseudomonic acid E, respectively. It should be noted that the limits for the test for *Related compounds* apply during the entire shelf-life of the Cream.

(PA7: L. Callahan) RTS—37476-2; 41278-2

Add the following:**▲Mupirocin Cream**

» Mupirocin Cream contains a quantity of Mupirocin Calcium equivalent to not less than 90.0 percent and not more than 120.0 percent of the

labeled amount of mupirocin ($C_{26}H_{44}O_9$). It may contain one or more suitable buffers, dispersants, and preservatives.

Packaging and storage—Preserve in collapsible tubes or well-closed containers. Store at 25°, excursions permitted between 15° and 30°.

Labeling—Label it to indicate that it contains Mupirocin Calcium and its equivalent content of mupirocin.

USP Reference standards (11)—*USP Mupirocin Lithium RS*.

Identification—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*.

Minimum fill (755): meets the requirements.

pH (791): between 6.0 and 8.0.

Microbial limits (61)—It meets the requirements of the tests for absence of *Staphylococcus aureus* and *Pseudomonas aeruginosa*. The total aerobic microbial count does not exceed 100 cfu per g.

Related compounds—

0.1 M Ammonium acetate, Solution A, Solution B, Mobile phase, pH 6.3 Phosphate buffer, and Chromatographic system—Proceed as directed in the *Assay*.

Sodium acetate solution—Add 5.8 mL of glacial acetic acid to 900 mL of water, adjust with sodium hydroxide TS to a pH of 4.0, dilute with water to 1000 mL, and mix.

Tetrahydrofuran solution—Mix 750 mL of tetrahydrofuran and 250 mL of water.

Sodium acetate and tetrahydrofuran solution—Prepare a mixture of *Sodium acetate solution* and *Tetrahydrofuran solution* (50 : 50).

Standard solution—Dissolve an accurately weighed portion of USP Mupirocin Lithium RS in *pH 6.3 Phosphate buffer*. Dilute an accurately measured volume of this solution quantitatively to obtain a solution containing 0.1 mg of mupirocin per mL.

Test stock solution—Transfer an accurately weighed quantity of Cream, equivalent to about 50 mg of mupirocin, to a screw-capped centrifuge tube. Add 5.0 mL of *Tetrahydrofuran solution*, cap, and disperse the Cream by mixing on a vortex mixer and shaking. Add 5.0 mL of *Sodium acetate solution*, cap, and mix. Centrifuge for about 15 minutes. Withdraw the lower layer from the tube, pass it through a filter having a 0.5- μ m or finer porosity, and use the filtrate.

Test solution—Transfer 1.0 mL of the *Test stock solution* to a 50-mL volumetric flask, dilute with *Sodium acetate and tetrahydrofuran solution* to volume, mix, and pass through a filter having a 0.5- μ m or finer porosity.

pH 4 Acetate buffer—Transfer about 13.6 g of sodium acetate to a 1000-mL volumetric flask, and dissolve in about 900 mL of water. Adjust with glacial acetic acid to a pH of 4.0, and dilute with water to volume.

Chromatographic system (see *Chromatography* (621))—Chromatograph the *Standard solution*, and record the peak responses as directed for *Procedure*: typical retention times are about 16 minutes for pseudomonic acid D and 21 minutes for mupirocin; the relative retention times are 0.36 for pseudomonic acid F, 0.6 for mupirocin degradation product A, 0.63 for mupirocin degradation product B, 0.74 for pseudomonic acid D, 0.9 for pseudomonic acid B, 1.0 for mupirocin, 1.15 for mupirocin related compound A, 1.23 for mupirocin related compound B, 2.03 for pseudomonic acid C, and 2.15–2.33 for pseudomonic acid E; the resolution, *R*, between pseudomonic acid D and mupirocin is not less than 3; the column efficiency for the mupirocin peak is not less

than 7000 theoretical plates; the tailing factor for the mupirocin peak is not more than 1.75; and the relative standard deviation of the mupirocin peak for replicate injections is not more than 2%.

Procedure—[NOTE—Ensure that buffers, dispersants, or preservatives in the formulation do not interfere with quantification of either impurities or degradation products.] Separately inject equal volumes (about 20 μ L) of the *Test stock solution* and the *Test solution* into the chromatograph, and measure the peak responses for all of the peaks that do not correspond to buffers, dispersants, or preservatives. Calculate the percentage of each related compound and degradation product relative to mupirocin in the portion of Cream taken by the formula:

$$2(r_i/r_m),$$

in which r_i is the peak response for each related compound or degradation product obtained from the *Test stock solution*; and r_m is the peak response of the mupirocin peak obtained from the *Test solution*: not more than 3.0% of pseudomonic acid D is found; not more than 8.5% of mupirocin degradation product A is found; not more than 16% of mupirocin degradation product B is found; not more than 1.2% of any other individual impurity or degradation product is found; and not more than 30% of total impurities and degradation products is found.

Assay—

0.1 M Ammonium acetate—Prepare as directed in the *Assay* under *Mupirocin Calcium*.

Solution A—Prepare a filtered and degassed mixture of *0.1 M Ammonium acetate* and tetrahydrofuran (75 : 25).

Solution B—Prepare a filtered and degassed mixture of *0.1 M Ammonium acetate* and tetrahydrofuran (70 : 30).

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system*. Make adjustments if necessary (see *System Suitability* under *Chromatography* (621)).

pH 6.3 Phosphate buffer—Dissolve 69 g of monobasic sodium phosphate in 800 mL of water, adjust with sodium hydroxide TS to pH 6.3, dilute with water to 1000 mL, and mix.

Standard preparation—Transfer about 21 mg of USP Mupirocin Lithium RS, accurately weighed, to a 200-mL volumetric flask, and dissolve in and dilute with *pH 6.3 Phosphate buffer* to volume.

Assay preparation—Transfer an accurately weighed quantity of Cream, equivalent to about 10 mg of mupirocin, to a 100-mL volumetric flask. Add 50 mL of *pH 6.3 Phosphate buffer* and 25 mL of tetrahydrofuran. Insert the stopper into the flask, mix on a vortex mixer, and shake for 1 to 3 minutes. Dilute with *pH 6.3 Phosphate buffer* to volume. Allow to stand until the oil layer separates out, then dilute the aqueous layer with *pH 6.3 Phosphate buffer* to volume. Repeat 2 to 3 times until as much of the oil layer has separated out as possible. After the final dilution, pass the final solution (bottom layer) through a filter having a 0.5- μ m or finer porosity.

Chromatographic system (see *Chromatography* (621))—The liquid chromatograph is equipped with a 240-nm detector and a 4.6-mm \times 25-cm column that contains 7- μ m packing L7. The flow rate is about 1 mL per minute. Maintain the column at a constant temperature up to 35°. The chromatograph is programmed as follows.

Time (minutes)	Solution A (%)	Solution B (%)	Elution
0	100	0	equilibration
0–6	100	0	isocratic
6–35	100→0	0→100	linear gradient
35–55	0	100	isocratic
55–55.01	0→100	100→0	immediate
55.01–65	100	0	isocratic

Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure*: typical retention times are about 16 minutes for pseudomonic acid D and 21 minutes for mupirocin; the resolution, *R*, between pseudomonic acid D and mupirocin is not less than 3; the column efficiency for the mupirocin peak is not less than 7000 theoretical plates; the tailing factor for the mupirocin peak is not more than 1.75; and the relative standard deviation of the mupirocin peak for replicate injections is not more than 2%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the peak area responses for the major peaks. Calculate the weight percent of mupirocin in the portion of Cream taken by the formula:

$$0.05E(M_s/M_u)(r_u/r_s),$$

in which M_s is the weight, in mg, of USP Mupirocin Lithium RS taken to prepare the *Standard preparation*; E is the designated mupirocin equivalent, in µg, of mupirocin in each mg of the USP Mupirocin Lithium RS; M_u is the weight, in mg, of Cream taken to prepare the *Assay preparation*;

and r_u and r_s are the mupirocin peak area responses obtained from the *Assay preparation* and the *Standard preparation*, respectively. [▲]USP29

BRIEFING

Paroxetine Tablets, USP 28 page 1476. It is proposed to revise *Identification test A* to specify the amount of hydrochloric acid used in the preparation of the *Test specimen*. The current procedure uses an inadequate amount of hydrochloric acid in the precipitation step. Also, it is proposed to revise *Identification test C* to change angular rotation to specific rotation.

(PA3: R. Ravichandran) RTS—42084-1

Paroxetine Tablets

[▲](Title for this new monograph—to become official February 1, 2006) [▲]USP28

Change to read:

Identification—

A: Infrared Absorption (197K)—

Test specimen—Transfer a quantity of finely powdered Tablets, equivalent to about 90 mg of paroxetine, to a suitable flask, add 100 mL of 0.1 N hydrochloric acid, and stir for 1 hour. Transfer the mixture to a separatory funnel, and add ammonium hydroxide until the solution is alkaline to litmus paper

[▲]1.5 mL of ammonium hydroxide to make the solution alkaline. [▲]USP29

Add 100 mL of ethyl ether to the funnel, and shake for 2 minutes. Transfer the organic layer into the necessary number of centrifuge tubes, and centrifuge for 10 minutes. Recombine the clarified extracts, add 1 drop of water and 0.5 mL of 0.1 N

[▲]USP29 hydrochloric acid, stir, and evaporate to dryness under a stream of nitrogen. Dry the residue in an oven at 90° for 1 hour.

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*.

C: Place a quantity of finely powdered Tablets, equivalent to about 450 mg of paroxetine, in a stoppered flask. Add 100 mL of alcohol, and shake for 1 hour. Centrifuge about 20 mL of the mixture, and measure the ~~angular~~