PRESCRIBING INFORMATION

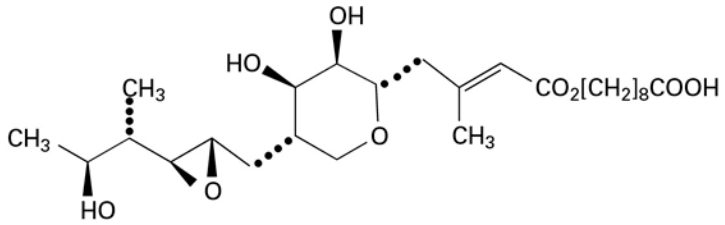
BACTROBAN® Ointment

(mupirocin ointment, 2%)

For Dermatologic Use

DESCRIPTION

Each gram of BACTROBAN Ointment (mupirocin ointment, 2%) contains 20 mg mupirocin in a bland water miscible ointment base (polyethylene glycol ointment, N.F.) consisting of polyethylene glycol 400 and polyethylene glycol 3350. Mupirocin is a naturally occurring antibiotic. The chemical name is (*E*)-(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-2*H*-pyran-2-crotonic acid, ester with 9-hydroxynonanoic acid. The molecular formula of mupirocin is $C_{26}H_{44}O_{9,}$ and the molecular weight is 500.63. The chemical structure is:



CLINICAL PHARMACOLOGY

Application of ^{14}C-labeled mupirocin ointment to the lower arm of normal male subjects followed by occlusion for 24 hours showed no measurable systemic absorption (<1.1 nanogram mupirocin per milliliter of whole blood). Measurable radioactivity was present in the stratum corneum of these subjects 72 hours after application.

Following intravenous or oral administration, mupirocin is rapidly metabolized. The principal metabolite, monic acid, is eliminated by renal excretion, and demonstrates no antibacterial activity. In a trial conducted in 7 healthy adult male subjects, the elimination half-life after intravenous administration of mupirocin was 20 to 40 minutes for mupirocin and 30 to 80 minutes for monic acid. The pharmacokinetics of mupirocin has not been studied in individuals with renal insufficiency.

Microbiology: Mupirocin is an antibacterial agent produced by fermentation using the organism *Pseudomonas fluorescens*. It is active against a wide range of gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA). It is also active against certain gram-negative bacteria. Mupirocin inhibits bacterial protein synthesis by reversibly and specifically binding to bacterial isoleucyl transfer-RNA synthetase. Due to this unique mode of action, mupirocin demonstrates no in vitro cross-resistance with other classes of antimicrobial agents.

Resistance occurs rarely. However, when mupirocin resistance does occur, it appears to result from the production of a modified isoleucyl-tRNA synthetase. High-level plasmid-mediated resistance (MIC >1,024 mcg/mL) has been reported in some strains of *S. aureus* and coagulase-negative staphylococci.

Mupirocin is bactericidal at concentrations achieved by topical administration. However, the minimum bactericidal concentration (MBC) against relevant pathogens is generally 8-fold to 30-fold higher than the minimum inhibitory concentration (MIC). In addition, mupirocin is highly protein-bound (>97%), and the effect of wound secretions on the MICs of mupirocin has not been determined.

Mupirocin has been shown to be active against most strains of *S. aureus* and *Streptococcus pyogenes*, both in vitro and in clinical trials (see INDICATIONS AND USAGE). The following in vitro data are available, BUT THEIR CLINICAL SIGNIFICANCE IS UNKNOWN. Mupirocin is active against most strains of *Staphylococcus epidermidis* and *Staphylococcus saprophyticus*.

INDICATIONS AND USAGE

BACTROBAN Ointment is indicated for the topical treatment of impetigo due to: *S. aureus* and *S. pyogenes*.

CONTRAINDICATIONS

This drug is contraindicated in patients with known hypersensitivity to any of the constituents of the product.

WARNINGS

Avoid contact with the eyes. In case of accidental contact, rinse well with water.

In the event of sensitization or severe local irritation from BACTROBAN Ointment, usage should be discontinued**.**

Clostridium difficile- associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including BACTROBAN, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing isolates of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial drug use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibacterial drug use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial treatment of *C. difficile,* and surgical evaluation should be instituted as clinically indicated.

PRECAUTIONS

As with other antibacterial products, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi.

BACTROBAN Ointment is not formulated for use on mucosal surfaces. Intranasal use has been associated with isolated reports of stinging and drying. A paraffin-based formulation — BACTROBAN® Nasal (mupirocin calcium ointment) — is available for intranasal use.

Polyethylene glycol can be absorbed from open wounds and damaged skin and is excreted by the kidneys. In common with other polyethylene glycol-based ointments, BACTROBAN Ointment should not be used in conditions where absorption of large quantities of polyethylene glycol is possible, especially if there is evidence of moderate or severe renal impairment.

BACTROBAN Ointment should not be used with intravenous cannulae or at central intravenous sites because of the potential to promote fungal infections and antimicrobial resistance.

Information for Patients: Use this medication only as directed by the healthcare provider. It is for external use only. Avoid contact with the eyes. If BACTROBAN Ointment gets in or near the eyes, rinse thoroughly with water. The medication should be stopped and the healthcare provider contacted if irritation, severe itching, or rash occurs.

If impetigo has not improved in 3 to 5 days, contact the healthcare provider.

Drug Interactions: The effect of the concurrent application of BACTROBAN Ointment and other drug products has not been studied.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals to evaluate carcinogenic potential of mupirocin have not been conducted.

Results of the following studies performed with mupirocin calcium or mupirocin sodium in vitro and in vivo did not indicate a potential for genotoxicity: Rat primary hepatocyte unscheduled DNA synthesis, sediment analysis for DNA strand breaks, *Salmonella* reversion test (Ames), *Escherichia coli* mutation assay, metaphase analysis of human lymphocytes, mouse lymphoma assay, and bone marrow micronuclei assay in mice.

Reproduction studies were performed in male and female rats with mupirocin administered subcutaneously at doses up to 14 times a human topical dose (approximately 60 mg mupirocin per day) on a mg/m^2 basis and revealed no evidence of impaired fertility and reproductive performance from mupirocin.

Pregnancy: *Teratogenic Effects:* Pregnancy Category B. Reproduction studies have been performed in rats and rabbits with mupirocin administered subcutaneously at doses up to 22 and 43 times, respectively, the human topical dose (approximately 60 mg mupirocin per day) on a mg/m^2 basis and revealed no evidence of harm to the fetus due to mupirocin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BACTROBAN Ointment is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of BACTROBAN Ointment have been established in the age range of 2 months to 16 years. Use of BACTROBAN Ointment in these age groups is supported by evidence from adequate and well-controlled trials of BACTROBAN Ointment in impetigo in pediatric subjects studied as a part of the pivotal clinical trials (see CLINICAL STUDIES).

ADVERSE REACTIONS

The following local adverse reactions have been reported in connection with the use of BACTROBAN Ointment: burning, stinging, or pain in 1.5% of subjects; itching in 1% of subjects; rash, nausea, erythema, dry skin, tenderness, swelling, contact dermatitis, and increased exudate in less than 1% of subjects.

Systemic allergic reactions, including anaphylaxis, urticaria, angioedema and generalized rash have been reported in patients treated with BACTROBAN formulations

DOSAGE AND ADMINISTRATION

A small amount of BACTROBAN Ointment should be applied to the affected area 3 times daily. The area treated may be covered with a gauze dressing if desired. Patients not showing a clinical response within 3 to 5 days should be re-evaluated.

CLINICAL STUDIES

The efficacy of topical BACTROBAN Ointment in impetigo was tested in 2 trials. In the first, subjects with impetigo were randomized to receive either BACTROBAN O or vehicle placebo 3 times daily for 8 to 12 days. Clinical efficacy rates at end of therapy in the evaluable populations (adults and pediatric subjects included) were 71% for BACTROBAN Ointment (n = 49) and 35% for vehicle placebo (n = 51). Pathogen eradication rates in the evaluable populations were 94% for BACTROBAN Ointment and 62% for vehicle placebo. There were no side effects reported in the group receiving BACTROBAN Ointment.

In the second trial, subjects with impetigo were randomized to receive either BACTROBAN Ointment 3 times daily or 30 to 40 mg/kg oral erythromycin ethylsuccinate per day (this was an unblinded trial) for 8 days. There was a follow-up visit 1 week after treatment ended. Clinical efficacy rates at the follow-up visit in the evaluable populations (adults and pediatric subjects included) were 93% for BACTROBAN Ointment (n = 29) and 78.5% for erythromycin (n = 28). Pathogen eradication rates in the evaluable populations were 100% for both test groups. There were no side effects reported in the group receiving BACTROBAN Ointment.

Pediatrics: There were 91 pediatric subjects aged 2 months to 15 years in the first trial described above. Clinical efficacy rates at end of therapy in the evaluable populations were 78% for BACTROBAN Ointment (n = 42) and 36% for vehicle placebo (n = 49). In the second trial described above, all subjects were pediatric except 2 adults in the group receiving

BACTROBAN Ointment. The age range of the pediatric subjects was 7 months to 13 years. The clinical efficacy rate for BACTROBAN Ointment (n = 27) was 96%, and for erythromycin it was unchanged (78.5%).

HOW SUPPLIED

BACTROBAN Ointment is supplied in 22-gram tubes.

NDC 0029-1525-44 (22-gram tube)

Store at controlled room temperature 20° to 25°C (68° to 77°F).

GlaxoSmithKline
Research Triangle Park, NC 27709

May/2014
BBM: xxPI

PRESCRIBING INFORMATION

BACTROBAN® Nasal

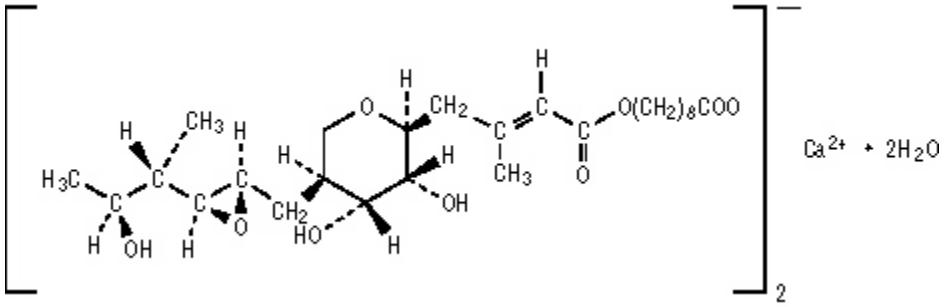
(mupirocin calcium ointment, 2%)

for intranasal use only

DESCRIPTION

BACTROBAN Nasal (mupirocin calcium ointment, 2%) contains the dihydrate crystalline calcium hemi-salt of the antibiotic mupirocin. Chemically, it is (α*E*,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-2*H*-pyran-2-crotonic acid, ester with 9-hydroxynonanoic acid, calcium salt (2:1), dihydrate.

The molecular formula of mupirocin calcium is $(C_{26}H_{43}O_9)_2Ca \cdot 2H_2O$, and the molecular weight is 1075.3. The molecular weight of mupirocin free acid is 500.6. The structural formula of mupirocin calcium is:



BACTROBAN Nasal is a white to off-white ointment that contains 2.15% w/w mupirocin calcium (equivalent to 2.0% pure mupirocin free acid) in a soft white ointment base. The inactive ingredients are paraffin and a mixture of glycerin esters (SOFTISAN® 649).

CLINICAL PHARMACOLOGY

Pharmacokinetics: Following single or repeated intranasal applications of 0.2 gram of BACTROBAN Nasal 3 times daily for 3 days to 5 healthy **adult** male subjects, no evidence of systemic absorption of mupirocin was demonstrated. The dosage regimen used in this trial was for pharmacokinetic characterization only (see DOSAGE AND ADMINISTRATION for proper clinical dosing information).

In this trial, the concentrations of mupirocin in urine and of monic acid in urine and serum were below the limit of determination of the assay for up to 72 hours after the applications. The lowest levels of determination of the assay used were 50 ng/mL of mupirocin in urine, 75 ng/mL of monic acid in urine, and 10 ng/mL of monic acid in serum. Based on the detectable limit of the urine assay for monic acid, one can extrapolate that a mean of 3.3% (range: 1.2 to 5.1%) of the applied dose could be systemically absorbed from the nasal mucosa of **adults**.

Data from a report of a pharmacokinetic trial in neonates and premature infants indicate that, unlike in adults, significant systemic absorption occurred following intranasal administration of BACTROBAN Nasal in this population. **At this time, the pharmacokinetic properties of mupirocin following intranasal application of BACTROBAN Nasal have not been**

adequately characterized in neonates or other children younger than 12 years, and in addition, the safety of the product in children younger than 12 years has not been established.

The effect of the concurrent application of intranasal mupirocin calcium ointment, 2% with other intranasal products has not been studied (see PRECAUTIONS, Drug Interactions).

Following intravenous or oral administration, mupirocin is rapidly metabolized. The principal metabolite, monic acid, demonstrates no antibacterial activity. In a trial conducted in 7 healthy adult male subjects, the elimination half-life after intravenous administration of mupirocin was 20 to 40 minutes for mupirocin and 30 to 80 minutes for monic acid. Monic acid is predominantly eliminated by renal excretion. The pharmacokinetics of mupirocin has not been studied in individuals with renal insufficiency.

Microbiology: Mupirocin is an antibacterial agent produced by fermentation using the organism *Pseudomonas fluorescens*.

Mechanism of Action: Mupirocin inhibits bacterial protein synthesis by reversibly and specifically binding to bacterial isoleucyl transfer-RNA synthetase.

Mupirocin is bactericidal at concentrations achieved by topical intranasal administration. Mupirocin is highly protein bound (>97%), and the effect of nasal secretions on the MICs of intranasally applied mupirocin has not been determined.

Mechanism of Resistance: When mupirocin resistance occurs, it results from the production of a modified isoleucyl-tRNA synthetase, or the acquisition of, by genetic transfer, a plasmid mediating a new isoleucyl-tRNA synthetase. High-level plasmid-mediated resistance (MIC >512 mcg/mL) has been reported in increasing numbers of isolates of *Staphylococcus aureus* and with higher frequency in coagulase-negative staphylococci. Mupirocin resistance occurs with greater frequency in methicillin-resistant than methicillin-susceptible staphylococci.

Cross Resistance: Due to its mode of action, mupirocin does not demonstrate cross-resistance with other classes of antimicrobial agents.

Susceptibility Testing: While it is suggested that isolates of *S. aureus* with a minimal inhibitory concentration (MIC) of <256 mcg/mL (absence of high level resistance to mupirocin) may be successfully eliminated from the nares, this criteria should be evaluated at each medical facility in conjunction with laboratory, medical and infection control staff.[1]

Correlation of Bactroban Nasal in vitro activity and MRSA nasal decolonization has been demonstrated in clinical trials (see CLINICAL STUDIES).

INDICATIONS AND USAGE

BACTROBAN Nasal is indicated for the eradication of nasal colonization with methicillin-resistant *S. aureus* in adult patients and health care workers as part of a comprehensive infection control program to reduce the risk of infection among patients at high risk of methicillin-resistant *S. aureus* infection during institutional outbreaks of infections with this pathogen.

NOTE:

1. There are insufficient data at this time to establish that this product is safe and effective as part of an intervention program to prevent autoinfection of high-risk patients from their own nasal colonization with *S. aureus*.
2. There are insufficient data at this time to recommend use of BACTROBAN Nasal for general prophylaxis of any infection in any patient population.
3. Greater than 90% of subjects/patients in clinical trials had eradication of nasal colonization 2 to 4 days after therapy was completed. Approximately 30% recolonization was reported in 1 domestic trial within 4 weeks after completion of therapy. These eradication rates were clinically and statistically superior to those reported in subjects in the vehicle-treated arms of the adequate and well-controlled trials. Those treated with vehicle had eradication rates of 5% to 30% at 2 to 4 days post-therapy with 85% to 100% recolonization within 4 weeks.

All adequate and well-controlled trials of this product were vehicle-controlled; therefore, no data from direct, head-to-head comparisons with other products are available at this time.

CONTRAINDICATIONS

BACTROBAN Nasal is contraindicated in patients with known hypersensitivity to any of the constituents of the product.

WARNINGS

AVOID CONTACT WITH THE EYES. In case of accidental contact, rinse well with water. Application of BACTROBAN Nasal to the eye under testing conditions has caused severe symptoms such as burning and tearing. These symptoms resolved within days to weeks after discontinuation of the ointment. In the event of a sensitization or severe local irritation from BACTROBAN Nasal, usage should be discontinued.

Clostridium difficile- associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including BACTROBAN, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing isolates of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial drug use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibacterial drug use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial treatment of *C. difficile,* and surgical evaluation should be instituted as clinically indicated.

PRECAUTIONS

General: As with other antibacterial products, prolonged use may result in overgrowth of nonsusceptible microorganisms, including fungi (see DOSAGE AND ADMINISTRATION).

Information for Patients: Patients should be given the following instructions:

- Apply approximately one-half of the ointment from the single-use tube directly into 1 nostril and the other half into the other nostril;
- Avoid contact of the medication with the eyes; if BACTROBAN Nasal gets in or near the eyes, rinse thoroughly with water.
- Discard the tube after using, do not re-use;
- Press the sides of the nose together and gently massage after application to spread the ointment throughout the inside of the nostrils; and
- Discontinue usage of the medication and call the healthcare practitioner if sensitization or severe local irritation occurs.

Drug Interactions: The effect of the concurrent application of intranasal mupirocin calcium and other intranasal products has not been studied. Until further information is known, mupirocin calcium ointment, 2% should not be applied concurrently with any other intranasal products.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals to evaluate carcinogenic potential of mupirocin calcium have not been conducted.

Results of the following studies performed with mupirocin calcium or mupirocin sodium in vitro and in vivo did not indicate a potential for mutagenicity: Rat primary hepatocyte unscheduled DNA synthesis, sediment analysis for DNA strand breaks, *Salmonella* reversion test (Ames), *Escherichia coli* mutation assay, metaphase analysis of human lymphocytes, mouse lymphoma assay, and bone marrow micronuclei assay in mice.

Reproduction studies were performed in rats with mupirocin administered subcutaneously at doses up to **40** times the human intranasal dose (approximately 20 mg mupirocin per day) on a mg/m^2 basis and revealed no evidence of impaired fertility from mupirocin sodium.

Pregnancy: *Teratogenic Effects:* Pregnancy Category B. Reproduction studies have been performed in rats and rabbits with mupirocin administered subcutaneously at doses up to 65 and 130 times, respectively, the human intranasal dose (approximately 20 mg mupirocin per day) on a mg/m^2 basis and revealed no evidence of harm to the fetus due to mupirocin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BACTROBAN Nasal is administered to a nursing woman.

Pediatric Use: Safety in children younger than 12 years has not been established (See CLINICAL PHARMACOLOGY).

ADVERSE REACTIONS

Clinical Trials: In clinical trials, 210 domestic and 2,130 foreign adult subjects received BACTROBAN Nasal ointment. Less than 1% of domestic or foreign subjects in clinical trials were withdrawn due to adverse events.

The most frequently reported adverse events in foreign clinical trials were as follows: rhinitis (1.0%), taste perversion (0.8%), pharyngitis (0.5%).

In domestic clinical trials, 17% (36/210) of adults treated with BACTROBAN Nasal ointment reported adverse events thought to be at least possibly drug-related. The incidence of adverse events that were reported in at least 1% of adults enrolled in domestic clinical trials were as follows:

Table 1. Adverse Events (≥1% Incidence) – Adults in US Trials

Adverse Events	% of Subjects Experiencing Event BACTROBAN Nasal (n = 210)
Headache	9%
Rhinitis	6%
Respiratory disorder, including upper respiratory tract congestion	5%
Pharyngitis	4%
Taste perversion	3%
Burning/stinging	2%
Cough	2%
Pruritus	1%

The following events thought possibly drug-related were reported in less than 1% of adults enrolled in domestic clinical trials: blepharitis, diarrhea, dry mouth, ear pain, epistaxis, nausea, and rash.

All adequate and well-controlled clinical trials have been performed using BACTROBAN Nasal ointment, 2% in 1 arm and the vehicle ointment in the other arm of the trial. No adequate and well-controlled safety data are available from direct, head-to-head comparative studies of this product and other products for this indication.

Systemic allergic reactions, including anaphylaxis, urticaria, angioedema and generalized rash have been reported in patients treated with BACTROBAN formulations.

OVERDOSAGE

Following single or repeated intranasal applications of BACTROBAN Nasal to adults, no evidence for systemic absorption of mupirocin was obtained. Intravenous infusions of 252 mg, as well as single oral doses of 500 mg of mupirocin, have been well tolerated in healthy adult

subjects. There is no information regarding local overdose of BACTROBAN Nasal or regarding oral ingestion of the nasal ointment formulation.

DOSAGE AND ADMINISTRATION

(See INDICATIONS AND USAGE.)

Adults (aged 12 years and older): Approximately one-half of the ointment from the single-use tube should be applied into 1 nostril and the other half into the other nostril twice daily (morning and evening) for 5 days.

After application, the nostrils should be closed by pressing together and releasing the sides of the nose repetitively for approximately 1 minute. This will spread the ointment throughout the nares.

The single-use 1.0-gram tube will deliver a total of approximately 0.5 grams of the ointment (approximately 0.25 grams/nostril).

The tube should be discarded after usage; it should not be re-used.

The safety and effectiveness of applications of this medication for greater than 5 days have not been established. There are no human clinical or pre-clinical animal data to support the use of this product in a chronic manner or in manners other than those described in this package insert.

Until further information is known, BACTROBAN Nasal should not be applied concurrently with any other intranasal products.

HOW SUPPLIED

BACTROBAN Nasal is supplied in 1.0-gram tubes.

NDC 0029-1526-11 (package of 10 single-tube cartons).

Store between 20° and 25°C (68° and 77°F); excursions permitted to 15°-30°C (59°-86°F). Do not refrigerate.

REFERENCE

1. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing; 22nd Informational Supplement. CLSI document M100-S22. CLSI, 950 West Valley Rd., Suite 2500, Wayne, PA, 19087, 2012.

GlaxoSmithKline
Research Triangle Park, NC 27709

May/2014

BBN:xxPI

PRESCRIBING INFORMATION

BACTROBAN® Cream

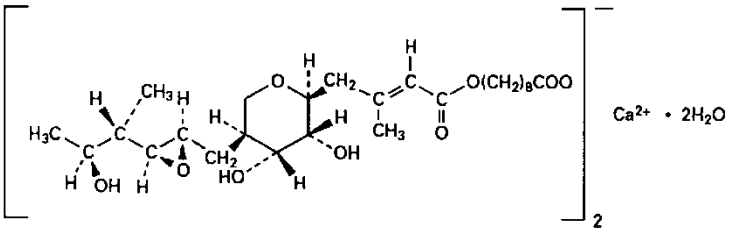
(mupirocin calcium cream, 2%)

For Dermatologic Use

DESCRIPTION

BACTROBAN Cream (mupirocin calcium cream, 2%) contains the dihydrate crystalline calcium hemi-salt of the antibiotic mupirocin. Chemically, it is (α*E*,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-2*H*-pyran-2-crotonic acid, ester with 9-hydroxynonanoic acid, calcium salt (2:1), dihydrate.

The molecular formula of mupirocin calcium is $(C_{26}H_{43}O_9)_2Ca \cdot 2H_2O$, and the molecular weight is 1075.3. The molecular weight of mupirocin free acid is 500.6. The structural formula of mupirocin calcium is:



BACTROBAN Cream is a white cream that contains 2.15% w/w mupirocin calcium (equivalent to 2.0% mupirocin free acid) in an oil and water-based emulsion. The inactive ingredients are benzyl alcohol, cetomacrogol 1000, cetyl alcohol, mineral oil, phenoxyethanol, purified water, stearyl alcohol, and xanthan gum.

CLINICAL PHARMACOLOGY

Pharmacokinetics: Systemic absorption of mupirocin through intact human skin is minimal. The systemic absorption of mupirocin was studied following application of BACTROBAN Cream 3 times daily for 5 days to various skin lesions (>10 cm in length or 100 cm^2 in area) in 16 adults (aged 29 to 60 years) and 10 children (aged 3 to 12 years). Some systemic absorption was observed as evidenced by the detection of the metabolite, monic acid, in urine. Data from this trial indicated more frequent occurrence of percutaneous absorption in children (90% of subjects) compared with adults (44% of subjects); however, the observed urinary concentrations in children (0.07 to 1.3 mcg/mL [1 pediatric subject had no detectable level]) are within the observed range (0.08 to 10.03 mcg/mL [9 adults had no detectable level]) in the adult population. In general, the degree of percutaneous absorption following multiple dosing appears to be minimal in adults and children. Any mupirocin reaching the systemic circulation is rapidly metabolized, predominantly to inactive monic acid, which is eliminated by renal excretion.

Microbiology: Mupirocin is an antibacterial agent produced by fermentation using the organism *Pseudomonas fluorescens*. It is active against a wide range of gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA). It is also active against certain gram-negative bacteria. Mupirocin inhibits bacterial protein synthesis by reversibly and

specifically binding to bacterial isoleucyl transfer-RNA synthetase. Due to this unique mode of action, mupirocin demonstrates no in vitro cross-resistance with other classes of antimicrobial agents.

Resistance occurs rarely; however, when mupirocin resistance does occur, it appears to result from the production of a modified isoleucyl-tRNA synthetase. High-level plasmid-mediated resistance (MIC >1,024 mcg/mL) has been reported in some strains of *Staphylococcus aureus* and coagulase-negative staphylococci.

Mupirocin is bactericidal at concentrations achieved by topical application. The minimum bactericidal concentration (MBC) against relevant pathogens is generally 8-fold to 30-fold higher than the minimum inhibitory concentration (MIC). In addition, mupirocin is highly protein bound (>97%), and the effect of wound secretions on the MICs of mupirocin has not been determined.

Mupirocin has been shown to be active against most strains of *S. aureus* and *Streptococcus pyogenes*, both in vitro and in clinical trials (see INDICATIONS AND USAGE). The following in vitro data are available, BUT THEIR CLINICAL SIGNIFICANCE IS UNKNOWN. Mupirocin is active against most strains of *Staphylococcus epidermidis* and *Staphylococcus saprophyticus*.

INDICATIONS AND USAGE

BACTROBAN Cream is indicated for the treatment of secondarily infected traumatic skin lesions (up to 10 cm in length or 100 cm^2 in area) due to susceptible strains of *S. aureus* and *S. pyogenes*.

CONTRAINDICATIONS

BACTROBAN Cream is contraindicated in patients with known hypersensitivity to any of the constituents of the product.

WARNINGS

Avoid contact with the eyes. In case of accidental contact, rinse well with water.

In the event of a sensitization or severe local irritation from BACTROBAN Cream, usage should be discontinued, and appropriate alternative therapy for the infection instituted.

Clostridium difficile- associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including BACTROBAN, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing isolates of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial drug use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibacterial drug use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

PRECAUTIONS

General: As with other antibacterial products, prolonged use may result in overgrowth of nonsusceptible microorganisms, including fungi (see DOSAGE AND ADMINISTRATION).

BACTROBAN Cream is not formulated for use on mucosal surfaces.

Information for Patients:

- Use this medication only as directed by the healthcare provider. It is for external use only. Avoid contact with the eyes. If BACTROBAN Cream gets in or near the eyes, rinse thoroughly with water.
- The treated area may be covered by gauze dressing if desired.
- Report to the healthcare provider any signs of local adverse reactions. The medication should be stopped and the healthcare provider contacted if irritation, severe itching, or rash occurs.
- If no improvement is seen in 3 to 5 days, contact the healthcare provider.

Drug Interactions: The effect of the concurrent application of topical mupirocin calcium cream and other topical products has not been studied.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals to evaluate carcinogenic potential of mupirocin calcium have not been conducted.

Results of the following studies performed with mupirocin calcium or mupirocin sodium in vitro and in vivo did not indicate a potential for mutagenicity: Rat primary hepatocyte unscheduled DNA synthesis, sediment analysis for DNA strand breaks, *Salmonella* reversion test (Ames), *Escherichia coli* mutation assay, metaphase analysis of human lymphocytes, mouse lymphoma assay, and bone marrow micronuclei assay in mice.

Fertility studies were performed in rats with mupirocin administered subcutaneously at doses up to 49 times a human topical dose of 1 gram/day (approximately 20 mg mupirocin per day) on a mg/m^2 basis and revealed no evidence of impaired fertility from mupirocin sodium.

Pregnancy: *Teratogenic Effects:* Pregnancy Category B. Teratology studies have been performed in rats and rabbits with mupirocin administered subcutaneously at doses up to 78 and 154 times, respectively, a human topical dose of 1 gram/day (approximately 20 mg mupirocin per day) on a mg/m^2 basis and revealed no evidence of harm to the fetus due to mupirocin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BACTROBAN Cream is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of BACTROBAN Cream have been established in the age groups 3 months to 16 years. Use of BACTROBAN Cream in these age groups is supported by evidence from adequate and well-controlled trials of BACTROBAN CREAM in adults with additional data from 93 pediatric subjects studied as part of the pivotal trials in adults (see CLINICAL STUDIES).

Geriatric Use: In 2 well-controlled trials, 30 subjects older than 65 years were treated with BACTROBAN Cream. No overall difference in the efficacy or safety of BACTROBAN Cream was observed in this patient population when compared with that observed in younger patients.

ADVERSE REACTIONS

In 2 randomized, double-blind, double-dummy trials, 339 subjects were treated with topical BACTROBAN Cream plus oral placebo. Adverse events thought to be possibly or probably drug-related occurred in 28 (8.3%) subjects. The incidence of those events that were reported in at least 1% of subjects enrolled in these trials were: headache (1.7%), rash, and nausea (1.1% each).

Other adverse events thought to be possibly or probably drug-related which occurred in less than 1% of subjects were: abdominal pain, burning at application site, cellulitis, dermatitis, dizziness, pruritus, secondary wound infection, and ulcerative stomatitis.

In a supportive trial in the treatment of secondarily infected eczema, 82 subjects were treated with BACTROBAN Cream. The incidence of adverse events thought to be possibly or probably drug-related was as follows: nausea (4.9%), headache, and burning at application site (3.6% each), pruritus (2.4%) and 1 report each of abdominal pain, bleeding secondary to eczema, pain secondary to eczema, hives, dry skin, and rash.

Systemic allergic reactions, including anaphylaxis, urticaria, angioedema and generalized rash have been reported in patients treated with BACTROBAN formulations.

OVERDOSAGE

Intravenous infusions of 252 mg, as well as single oral doses of 500 mg of mupirocin, have been well tolerated in healthy adult subjects. There is no information regarding overdose of BACTROBAN Cream.

DOSAGE AND ADMINISTRATION

A small amount of BACTROBAN Cream should be applied to the affected area 3 times daily for 10 days. The area treated may be covered with gauze dressing if desired. Patients not showing a clinical response within 3 to 5 days should be re-evaluated.

CLINICAL STUDIES

The efficacy of topical BACTROBAN Cream for the treatment of secondarily infected traumatic skin lesions (e.g., lacerations, sutured wounds, and abrasions not more than 10 cm in length or 100 cm^2 in total area) was compared with that of oral cephalexin in 2 randomized, double-blind, double-dummy clinical trials. Clinical efficacy rates at follow-up in the per-

protocol populations (adults and pediatric subjects included) were 96.1% for BACTROBAN Cream (n = 231) and 93.1% for oral cephalexin (n = 219). Pathogen eradication rates at follow-up in the per-protocol populations were 100% for both BACTROBAN Cream and oral cephalexin.

Pediatrics: There were 93 pediatric subjects aged 2 weeks to 16 years enrolled per protocol in the secondarily infected skin lesion trials, although only 3 were less than 2 years of age in the population treated with BACTROBAN Cream. Subjects were randomized to either 10 days of topical BACTROBAN Cream 3 times daily or 10 days of oral cephalexin (250 mg 4 times daily for subjects >40 kg or 25 mg/kg/day oral suspension in 4 divided doses for subjects ≤40 kg). Clinical efficacy at follow-up (7 to 12 days post-therapy) in the per-protocol populations was 97.7% (43/44) for BACTROBAN Cream and 93.9% (46/49) for cephalexin. Only 1 adverse event (headache) was thought to be possibly or probably related to drug therapy with BACTROBAN Cream in the intent-to-treat pediatric population of 70 children (1.4%).

HOW SUPPLIED

BACTROBAN Cream is supplied in 15-gram and 30-gram tubes.

NDC 0029-1527-22 (15-gram tube)

NDC 0029-1527-25 (30-gram tube)

Store at or below 25°C (77°F). Do not freeze.

GlaxoSmithKline

Research Triangle Park, NC 27709

May/2014

BBC:xxPI