PRESCRIBING INFORMATION

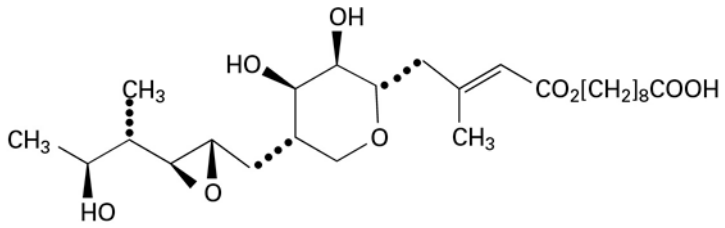
BACTROBAN® Ointment

(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*. Mupirocin inhibits bacterial protein synthesis by reversibly and specifically binding to bacterial isoleucyl transfer-RNA (tRNA) synthetase. Due to this unique mode of action, mupirocin does not demonstrate cross-resistance with other classes of antimicrobial agents.

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. Because of the occurrence of mupirocin resistance in methicillin-resistant *Staphylococcus aureus* (MRSA), it is appropriate to test MRSA populations for mupirocin susceptibility prior to the use of mupirocin using a standardized method.[1,2,3]

Mupirocin is bactericidal at concentrations achieved by topical administration. 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 susceptible 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 isolates of *Staphylococcus epidermidis*.

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 formulations of BACTROBAN.

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 Ointment 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).

REFERENCES

1. Clinical and Laboratory Standards Institute (CLSI). Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard - Tenth Edition. CLSI document M07-A10 [2015], Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA.

2. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Disk Diffusion Susceptibility Tests; Approved Standard – Twelfth Edition. CLSI document M02-A12 [2015], Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA.

3. Finlay JE, Miller LA, Poupard JA. Interpretive criteria for testing susceptibility of staphylococci to mupirocin. *Antimicrob Agents Chemother* 1997;41(5):1137-1139.

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