

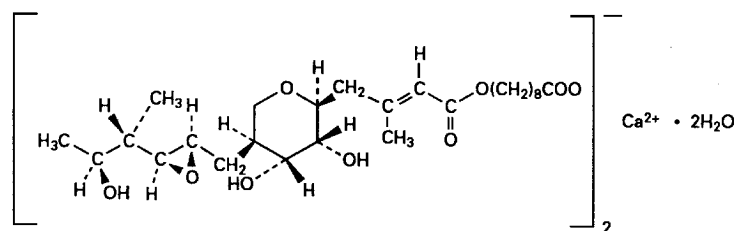
PRESCRIBING INFORMATION

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 ($\alpha E, 2S, 3R, 4R, 5S$)-5-[($2S, 3S, 4S, 5S$)-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.

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 cm² 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*. Mupirocin inhibits bacterial protein synthesis by reversibly

35 and specifically binding to bacterial isoleucyl transfer-RNA (tRNA) synthetase. Due to this
36 unique mode of action, mupirocin does not demonstrate cross-resistance with other classes of
37 antimicrobial agents.

38 When mupirocin resistance occurs, it results from the production of a modified
39 isoleucyl-tRNA synthetase, or the acquisition of, by genetic transfer, a plasmid mediating a new
40 isoleucyl-tRNA synthetase. High-level plasmid-mediated resistance (MIC >512 mcg/mL) has
41 been reported in increasing numbers of isolates of *Staphylococcus aureus* and with higher
42 frequency in coagulase-negative staphylococci. Mupirocin resistance occurs with greater
43 frequency in methicillin-resistant than methicillin-susceptible staphylococci. Because of the
44 occurrence of mupirocin resistance in methicillin-resistant *Staphylococcus aureus* (MRSA), it is
45 appropriate to test MRSA populations for mupirocin susceptibility prior to the use of mupirocin
46 using a standardized method.^{1,2,3}

47 Mupirocin is bactericidal at concentrations achieved by topical application. Mupirocin is
48 highly protein bound (>97%), and the effect of wound secretions on the MICs of mupirocin has
49 not been determined.

50 Mupirocin has been shown to be active against susceptible strains of *S. aureus* and
51 *Streptococcus pyogenes*, both in vitro and in clinical trials (see INDICATIONS AND USAGE).
52 The following in vitro data are available, **but their clinical significance is unknown**. Mupirocin
53 is active against most isolates of *Staphylococcus epidermidis*.

54 **INDICATIONS AND USAGE**

55 BACTROBAN Cream is indicated for the treatment of secondarily infected traumatic skin
56 lesions (up to 10 cm in length or 100 cm² in area) due to susceptible strains of *S. aureus* and *S.*
57 *pyogenes*.

58 **CONTRAINDICATIONS**

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

61 **WARNINGS**

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

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

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

69 *C. difficile* produces toxins A and B which contribute to the development of CDAD.
70 Hypertoxin-producing isolates of *C. difficile* cause increased morbidity and mortality, as these
71 infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be
72 considered in all patients who present with diarrhea following antibacterial drug use. Careful

73 medical history is necessary since CDAD has been reported to occur over 2 months after the
74 administration of antibacterial agents.

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

79 **PRECAUTIONS**

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

82 BACTROBAN Cream is not formulated for use on mucosal surfaces.

83 **Information for Patients:**

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

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

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

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

100 Fertility studies were performed in rats with mupirocin administered subcutaneously at doses
101 up to 49 times a human topical dose of 1 gram/day (approximately 20 mg mupirocin per day) on
102 a mg/m² basis and revealed no evidence of impaired fertility from mupirocin sodium.

103 **Pregnancy: Teratogenic Effects:** Pregnancy Category B. Teratology studies have been
104 performed in rats and rabbits with mupirocin administered subcutaneously at doses up to 78 and
105 154 times, respectively, a human topical dose of 1 gram/day (approximately 20 mg mupirocin
106 per day) on a mg/m² basis and revealed no evidence of harm to the fetus due to mupirocin. There
107 are, however, no adequate and well-controlled studies in pregnant women. Because animal
108 reproduction studies are not always predictive of human response, this drug should be used
109 during pregnancy only if clearly needed.

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

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

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

121 **ADVERSE REACTIONS**

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

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

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

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

137 **OVERDOSAGE**

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

141 **DOSAGE AND ADMINISTRATION**

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

145 **CLINICAL STUDIES**

146 The efficacy of topical BACTROBAN Cream for the treatment of secondarily infected
147 traumatic skin lesions (e.g., lacerations, sutured wounds, and abrasions not more than 10 cm in
148 length or 100 cm² in total area) was compared with that of oral cephalexin in 2 randomized,
149 double-blind, double-dummy clinical trials. Clinical efficacy rates at follow-up in the per
150 protocol populations (adults and pediatric subjects included) were 96.1% for BACTROBAN
151 Cream (n = 231) and 93.1% for oral cephalexin (n = 219). Pathogen eradication rates at
152 follow-up in the per-protocol populations were 100% for both BACTROBAN Cream and oral
153 cephalexin.

154 **Pediatrics:** There were 93 pediatric subjects aged 2 weeks to 16 years enrolled per protocol in
155 the secondarily infected skin lesion trials, although only 3 were less than 2 years of age in the
156 population treated with BACTROBAN Cream. Subjects were randomized to either 10 days of
157 topical BACTROBAN Cream 3 times daily or 10 days of oral cephalexin (250 mg 4 times daily
158 for subjects >40 kg or 25 mg/kg/day oral suspension in 4 divided doses for subjects ≤40 kg).
159 Clinical efficacy at follow-up (7 to 12 days post-therapy) in the per-protocol populations was
160 97.7% (43/44) for BACTROBAN Cream and 93.9% (46/49) for cephalexin. Only 1 adverse
161 event (headache) was thought to be possibly or probably related to drug therapy with
162 BACTROBAN Cream in the intent-to-treat pediatric population of 70 children (1.4%).

163 **HOW SUPPLIED**

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

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

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

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

168 **REFERENCES**

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180
181 GlaxoSmithKline

182 Research Triangle Park, NC 27709

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