MUPIROCIN- mupirocin calcium cream
Glenmark Generics Inc., USA

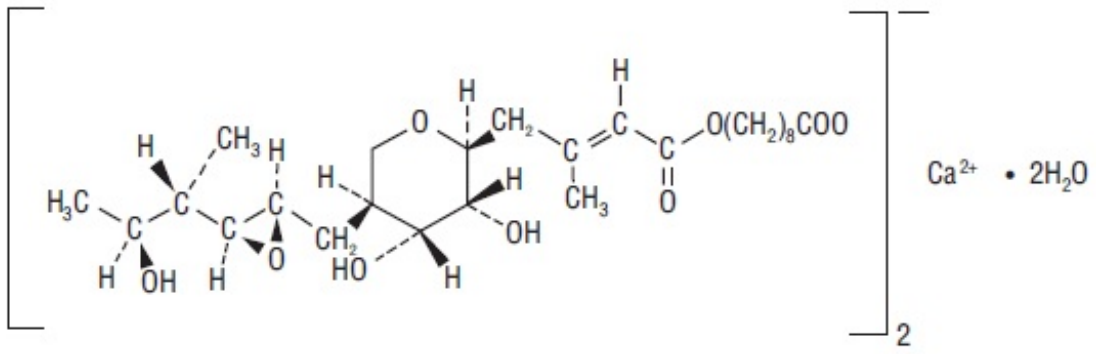
MUPIROCIN Cream USP, 2%

PRESCRIBING INFORMATION
For Dermatologic Use
Rx Only

DESCRIPTION

Mupirocin cream USP, 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-2H-pyran-2-crotonic acid, ester with 9-hydroxynonanoic acid, calcium salt (2:1), dihydrate.

The molecular formula of mupirocin calcium USP 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 USP is:



Mupirocin cream USP, 2% is a white cream that contains 2.15% w/w mupirocin calcium USP (equivalent to 2.0% mupirocin free acid) in an oil and water-based emulsion. The inactive ingredients are benzyl alcohol, glycerol monostearate, mineral oil, phenoxyethanol, polyoxyl 20 cetostearyl ether, purified water 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 mupirocin cream three 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 - 1.3 mcg/mL [1 pediatric patient had no detectable level]) are within the observed range (0.08 - 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

Mupirocin cream USP, 2 % 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

Mupirocin 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 mupirocin 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 mupirocin, 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**).

Mupirocin cream is not formulated for use on mucosal surfaces.

Information for patients

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

Pediatric use

The safety and effectiveness of mupirocin cream have been established in the age groups 3 months to 16 years. Use of mupirocin cream in these age groups is supported by evidence from adequate and well-controlled studies of mupirocin cream in adults with additional data from 93 pediatric patients

studied as part of the pivotal trials in adults. (See **CLINICAL STUDIES**).

Geriatric use

In 2 well-controlled studies, 30 patients older than 65 years were treated with mupirocin cream. No overall difference in the efficacy or safety of mupirocin cream was observed in this patient population when compared to that observed in younger patients.

ADVERSE REACTIONS

In 2 randomized, double-blind, double-dummy trials, 339 subjects were treated with topical mupirocin 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 mupirocin 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 mupirocin 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 mupirocin cream.

DOSAGE AND ADMINISTRATION

A small amount of mupirocin cream USP 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 mupirocin 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 to 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 mupirocin 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 mupirocin 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 mupirocin cream. Subjects were randomized to either 10 days of topical mupirocin 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 mupirocin 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 mupirocin cream in the intent-to-treat pediatric population of 70 children (1.4%).

HOW SUPPLIED

Mupirocin cream USP, 2% is supplied in 15 gram and 30 gram tubes.

NDC 68462-564-17 15 gram tube (1 tube per carton)

NDC 68462-564-35 30 gram tube (1 tube per carton)

Store at 20º to 25ºC (68º to 77ºF) [see USP Controlled Room Temperature]. Do not freeze.

Manufactured by:

Glenmark Generics Ltd.
Colvale-Bardez, Goa 403 513, India

Manufactured for:

Glenmark Generics Inc., USA
Mahwah, NJ 07430

Questions? 1 (888)721-7115
www.glenmarkgenerics.com

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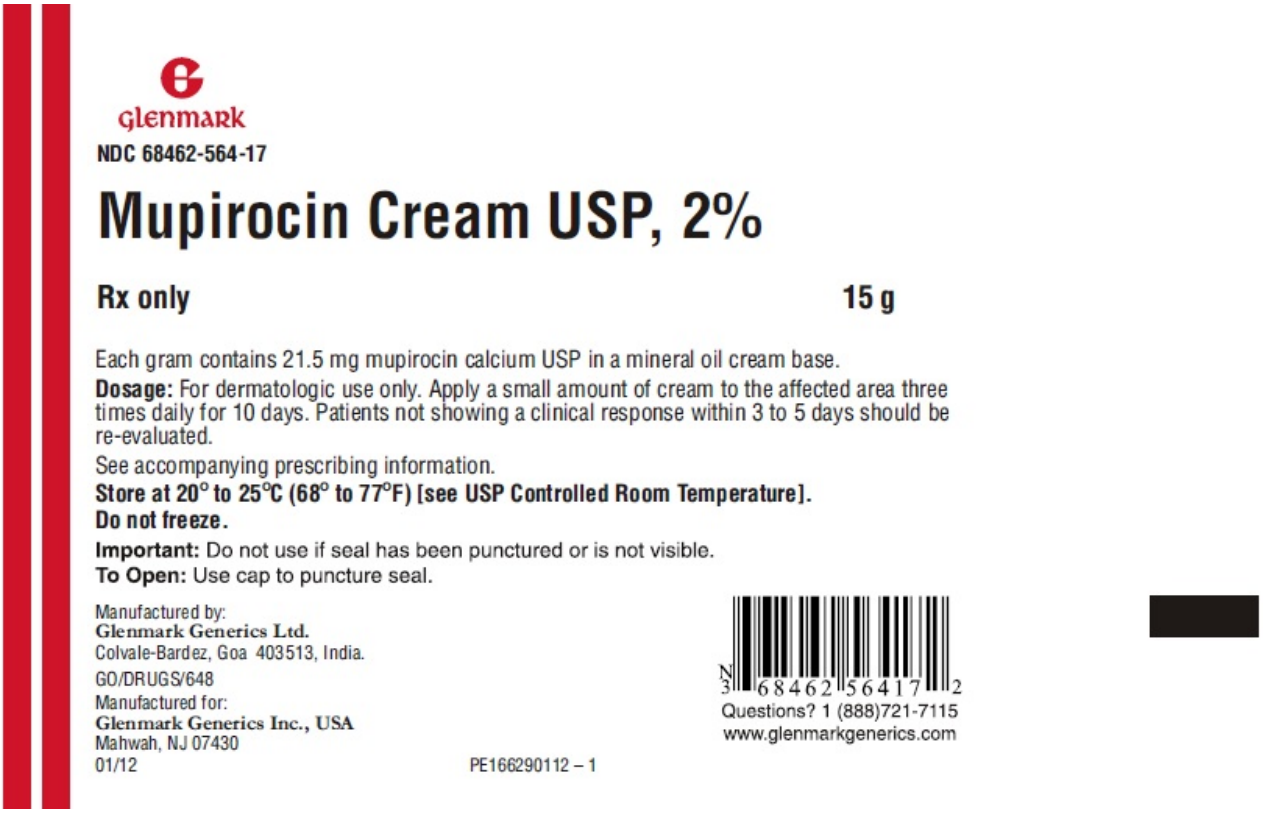
Principal Display Panel

NDC 68462-564-17

Mupirocin Cream USP, 2% - 15 g



MUPIROCIN

mupirocin cream

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:68462-564
Route of Administration	TOPICAL	**DEA Schedule**	

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
MUPIROCIN CALCIUM (MUPIROCIN)	MUPIROCIN	2 g in 100 g

Inactive Ingredients	
Ingredient Name	**Strength**
MINERAL OIL	
PHENOXYETHANOL	
WATER	
XANTHAN GUM	
BENZYL ALCOHOL	
POLYOXYL 20 CETOSTEARYL ETHER	
GLYCERYL MONOSTEARATE	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68462-564-17	15 g in 1 TUBE		
2	NDC:68462-564-35	30 g in 1 TUBE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA201587	01/24/2013	

Labeler - Glenmark Generics Inc., USA (130597813)

Establishment

Name	Address	ID/FEI	Business Operations
Glenmark Generics Limited		677318665	ANALYSIS(68462-564), MANUFACTURE(68462-564)

Revised: 6/2014 Glenmark Generics Inc., USA