LOPROX® CREAM
(ciclopirox) 0.77%

FOR DERMATOLOGIC USE ONLY.
NOT FOR USE IN EYES.

Rx Only

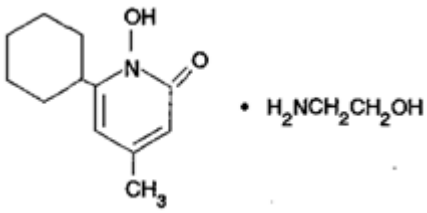
DESCRIPTION

LOPROX® Cream (ciclopirox) 0.77% is for topical use.

Each gram of LOPROX® Cream contains 7.70 mg of ciclopirox (as ciclopirox olamine) in a water miscible vanishing cream base consisting of purified water USP, cetyl alcohol NF, light mineral oil NF, octyldodecanol NF, stearyl alcohol NF, polysorbate 60 NF, myristyl alcohol, sorbitan monostearate NF, lactic acid USP, and benzyl alcohol NF (1%) as preservative.

LOPROX® Cream contains a synthetic, broad-spectrum, antifungal agent ciclopirox (as ciclopirox olamine). The chemical name is 6-cyclohexyl-1-hydroxy-4-methyl-2(1*H*)-pyridone, 2-aminoethanol salt.

The CAS Registry Number is 41621-49-2. The chemical structure is:



CLINICAL PHARMACOLOGY

Mechanism of Action

Ciclopirox is a hydroxypyridone antifungal agent that acts by chelation of polyvalent cations (Fe^{3+} or Al^{3+}), resulting in the inhibition of the metal-dependent enzymes that are responsible for the degradation of peroxides within the fungal cell.

Pharmacokinetics

Pharmacokinetic studies in men with tagged ciclopirox solution in polyethylene glycol 400 showed an average of 1.3% absorption of the dose when it was applied topically to 750 cm^2 on the back followed by occlusion for 6 hours. The biological half-life was 1.7 hours and excretion occurred via the kidney. Two days after application only 0.01% of the dose applied could be found in the urine. Fecal excretion was negligible.

Penetration studies in human cadaverous skin from the back, with LOPROX® Cream with tagged ciclopirox showed the presence of 0.8 to 1.6% of the dose in the stratum corneum 1.5 to 6 hours after application. The levels in the dermis were still 10 to 15 times above the minimum inhibitory concentrations.

Autoradiographic studies with human cadaverous skin showed that ciclopirox penetrates into the hair and through the epidermis and hair follicles into the sebaceous glands and dermis, while a portion of the drug remains in the stratum corneum.

Draize Human Sensitization Assay, 21-Day Cumulative Irritancy study, Phototoxicity study, and Photo-Draize study conducted in a total of 142 healthy male subjects showed no contact sensitization of the delayed hypersensitivity type, no irritation, no phototoxicity, and no photo-contact sensitization due to LOPROX® Cream.

INDICATIONS AND USAGE

LOPROX® Cream is indicated for the topical treatment of the following dermal infections: tinea pedis, tinea cruris, and tinea corporis due to *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Epidermophyton floccosum*, and *Microsporum canis;* candidiasis (moniliasis) due to *Candida albicans*; and tinea (pityriasis) versicolor due to *Malassezia furfur*.

CONTRAINDICATIONS

LOPROX® Cream is contraindicated in individuals who have shown hypersensitivity to any of its components.

WARNINGS

LOPROX® Cream is not for ophthalmic use.
Keep out of reach of children.

PRECAUTIONS

If a reaction suggesting sensitivity or chemical irritation should occur with the use of LOPROX® Cream, treatment should be discontinued and appropriate therapy instituted.

Information for Patients

The patient should be told to:

1. Use the medication for the full treatment time even though symptoms may have improved and notify the physician if there is no improvement after four weeks.
2. Inform the physician if the area of application shows signs of increased irritation (redness, itching, burning, blistering, swelling, or oozing) indicative of possible sensitization.
3. Avoid the use of occlusive wrappings or dressings.

Carcinogenesis, Mutagenesis, Impairment of Fertility

A 104-week dermal carcinogenicity study in mice was conducted with ciclopirox cream applied at doses up to 1.93% (100 mg/kg/day or 300 mg/m^2/day). No increase in drug related neoplasms was noted when compared to control.

The following in vitro genotoxicity tests have been conducted with ciclopirox: evaluation of gene mutation in the Ames Salmonella and E. coli assays (negative); chromosome aberration assays in V79 Chinese hamster lung fibroblast cells, with and without metabolic activation (positive); chromosome aberration assays in V79 Chinese hamster lung fibroblast cells in the presence of supplemental Fe^{3+}, with and without metabolic activation (negative); gene mutation assays in the HGPRT-test with V79 Chinese hamster lung fibroblast cells (negative); and a primary DNA damage assay (i.e., unscheduled DNA synthesis assay in A549 human cells) (negative). An in vitro cell transformation assay in BALB/c 3T3 cells was negative for cell transformation. In an in vivo Chinese hamster bone marrow cytogenetic assay, ciclopirox was negative for chromosome aberrations at a dosage of 5000 mg/kg body weight.

A combined oral fertility and embryofetal developmental study was conducted in rats with ciclopirox olamine. No effect on fertility or reproductive performance was noted at the highest dose tested of 3.85

mg/kg/day ciclopirox (approximately 1.2 times the maximum recommended human dose based on body surface area comparisons).

Pregnancy

Teratogenic Effects: Pregnancy Category B

There are no adequate or well-controlled studies in pregnant women. Therefore, LOPROX Cream should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Oral embryofetal developmental studies were conducted in mice, rats, rabbits and monkeys. Ciclopirox or ciclopirox olamine was orally administered during the period of organogenesis. No maternal toxicity, embryotoxicity or teratogenicity were noted at the highest doses of 77, 125, 80 and 38.5 mg/kg/day ciclopirox in mice, rats, rabbits and monkeys, respectively (approximately 11, 37, 51 and 24 times the maximum recommended human dose based on body surface area comparisons, respectively).

Dermal embryofetal developmental studies were conducted in rats and rabbits with ciclopirox olamine dissolved in PEG 400. Ciclopirox olamine was topically administered during the period of organogenesis. No maternal toxicity, embryotoxicity or teratogenicity were noted at the highest doses of 92 mg/kg/day and 77 mg/kg/day ciclopirox in rats and rabbits, respectively (approximately 27 and 49 times the maximum recommended human dose based on body surface area comparisons, respectively).

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 LOPROX® Cream is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 10 years have not been established.

ADVERSE REACTIONS

In all controlled clinical studies with 514 patients using LOPROX® Cream and in 296 patients using the vehicle cream, the incidence of adverse reactions was low. This included pruritus at the site of application in one patient and worsening of the clinical signs and symptoms in another patient using ciclopirox cream and burning in one patient and worsening of the clinical signs and symptoms in another patient using the vehicle cream.

DOSAGE AND ADMINISTRATION

Gently massage LOPROX® Cream into the affected and surrounding skin areas twice daily, in the morning and evening. Clinical improvement with relief of pruritus and other symptoms usually occurs within the first week of treatment. If a patient shows no clinical improvement after four weeks of treatment with LOPROX® Cream, the diagnosis should be redetermined. Patients with tinea versicolor usually exhibit clinical and mycological clearing after two weeks of treatment.

HOW SUPPLIED

LOPROX® Cream (ciclopirox) 0.77% is supplied in 15 gram (NDC 99207-015-15), 30 gram (NDC 99207-015-30), and 90 gram (NDC 99207-015-90) tubes.

Store at 15º - 30ºC (59º - 86ºF).

Manufactured for:
Medicis, The Dermatology Company
Scottsdale, AZ 85256
by: Patheon, Inc.

Mississauga, Ontario L5N 7K9
CANADA

Made in Canada

Prescribing Information as of 06/2013.

10100302

LOPROX®

TOPICAL SUSPENSION

(ciclopirox) 0.77% (w/w)

FOR DERMATOLOGIC USE ONLY.

NOT FOR USE IN EYES.

Rx Only

DESCRIPTION

LOPROX® Topical Suspension 0.77% (ciclopirox) is for topical use.

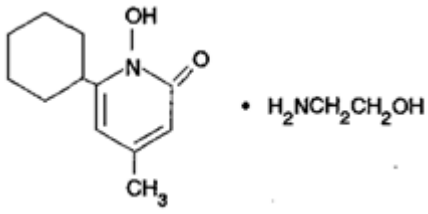
Each gram of LOPROX Topical Suspension contains 7.70 mg of ciclopirox (as ciclopirox olamine) in a water miscible suspension base consisting of purified water USP, cocamide DEA, octyldodecanol NF, mineral oil USP, stearyl alcohol NF, cetyl alcohol NF, polysorbate 60 NF, myristyl alcohol NF, lactic acid USP, sorbitan monostearate NF, and benzyl alcohol NF (1%) as preservative.

LOPROX® Topical Suspension contains a synthetic, broad-spectrum, antifungal agent ciclopirox (as ciclopirox olamine). The chemical name is 6-cyclohexyl-1 -hydroxy-4-methyl-2(1*H*)-pyridone, 2-aminoethanol salt.

The CAS Registry Number is 41621-49-2.

LOPROX® Topical Suspension has a pH of 7.

The chemical structure is:



CLINICAL PHARMACOLOGY

Mechanism of Action

Ciclopirox is a hydroxypyridone antifungal agent that acts by chelation of polyvalent cations (Fe^{3+} or Al^{3+}), resulting in the inhibition of the metal-dependent enzymes that are responsible for the degradation of peroxides within the fungal cell.

Pharmacokinetics

Pharmacokinetic studies in men with radiolabeled ciclopirox solution in polyethylene glycol 400 showed an average of 1.3% absorption of the dose when it was applied topically to 750 cm^2 on

the back followed by occlusion for 6 hours. The biological half-life was 1.7 hours and excretion occurred via the kidney. Two days after application only 0.01% of the dose applied could be found in the urine. Fecal excretion was negligible. Autoradiographic studies with human cadaver skin showed that ciclopirox penetrates into the hair and through the epidermis and hair follicles into the sebaceous glands and dermis, while a portion of the drug remains in the stratum corneum.

In vitro penetration studies in frozen or fresh excised human cadaver and pig skin indicated that the penetration of LOPROX® Topical Suspension is equivalent to that of LOPROX® Cream (ciclopirox olamine) 0.77%. Therapeutic equivalence of cream and suspension formulations also was indicated by studies of experimentally induced guinea pig and human trichophytosis.

INDICATIONS AND USAGE

LOPROX® Topical Suspension is indicated for the topical treatment of the following dermal infections: tinea pedis, tinea cruris and tinea corporis due to *Trichophyton rubrum, Trichophyton mentagrophytes, Epidermophyton floccosum,* and *Microsporum canis;* cutaneous candidiasis (moniliasis) due to *Candida albicans;* and tinea (pityriasis) versicolor due to *Malassezia furfur.*

CONTRAINDICATIONS

LOPROX® Topical Suspension is contraindicated in individuals who have shown hypersensitivity to any of its components.

WARNINGS

General

LOPROX® Topical Suspension is not for ophthalmic use.

Keep out of reach of children.

PRECAUTIONS

If a reaction suggesting sensitivity or chemical irritation should occur with the use of LOPROX® Topical Suspension, treatment should be discontinued and appropriate therapy instituted.

Information for Patients

The patient should be told to:

1. Use the medication for the full treatment time even though signs/symptoms may have improved and notify the physician if there is no improvement after four weeks.
2. Inform the physician if the area of application shows signs of increased irritation (redness, itching, burning, blistering, swelling, oozing) indicative of possible sensitization.
3. Avoid the use of occlusive wrappings or dressings.

Carcinogenesis, Mutagenesis, Impairment of Fertility

A 104-week dermal carcinogenicity study in mice was conducted with ciclopirox cream applied at doses up to 1.93% (100 mg/kg/day or 300 mg/m^2/day). No increase in drug related neoplasms was noted when compared to control.

The following in vitro genotoxicity tests have been conducted with ciclopirox: evaluation of gene mutation in the Ames Salmonella and E. coli assays (negative); chromosome aberration assays in V79 Chinese hamster lung fibroblast cells, with and without metabolic activation (positive); chromosome aberration assays in V79 Chinese hamster lung fibroblast cells in the presence of supplemental Fe^{3+}, with and without metabolic activation (negative); gene mutation assays in the HGPRT-test with V79 Chinese hamster lung fibroblast cells (negative); and a primary DNA damage assay (i.e., unscheduled DNA synthesis assay in A549 human cells) (negative). An in vitro cell transformation assay in BALB/c 3T3 cells was negative for cell transformation. In an in vivo Chinese hamster bone marrow cytogenetic assay, ciclopirox was negative for chromosome aberrations at a dosage of 5000 mg/kg body weight.

A combined oral fertility and embryofetal developmental study was conducted in rats with ciclopirox olamine. No effect on fertility or reproductive performance was noted at the highest dose tested of 3.85 mg/kg/day ciclopirox (approximately 1.2 times the maximum recommended human dose based on body surface area comparisons).

Pregnancy

Teratogenic Effects: Pregnancy Category B

There are no adequate or well-controlled studies in pregnant women. Therefore, LOPROX Topical Suspension should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Oral embryofetal developmental studies were conducted in mice, rats, rabbits and monkeys. Ciclopirox or ciclopirox olamine was orally administered during the period of organogenesis. No maternal toxicity, embryotoxicity or teratogenicity were noted at the highest doses of 77, 125, 80 and 38.5 mg/kg/day ciclopirox in mice, rats, rabbits and monkeys, respectively (approximately 11, 37, 51 and 24 times the maximum recommended human dose based on body surface area comparisons, respectively).

Dermal embryofetal developmental studies were conducted in rats and rabbits with ciclopirox olamine dissolved in PEG 400. Ciclopirox olamine was topically administered during the period of organogenesis. No maternal toxicity, embryotoxicity or teratogenicity were noted at the highest doses of 92 mg/kg/day and 77 mg/kg/day ciclopirox in rats and rabbits, respectively (approximately 27 and 49 times the maximum recommended human dose based on body surface area comparisons, respectively).

Nursing Mothers

It is not known whether this drug is excreted in human milk. Caution should be exercised when LOPROX® Topical Suspension is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 10 years have not been established.

ADVERSE REACTIONS

In the controlled clinical trial with 89 patients using LOPROX® Topical Suspension and 89 patients using the vehicle, the incidence of adverse reactions was low. Those considered possibly related to treatment or occurring in more than one patient were pruritus, which occurred in two patients using ciclopirox suspension and one patient using the suspension vehicle, and burning, which occurred in one patient using ciclopirox suspension.

DOSAGE AND ADMINISTRATION

Gently massage LOPROX® Topical Suspension into the affected and surrounding skin areas twice daily, in the morning and evening. Clinical improvement with relief of pruritus and other symptoms usually occurs within the first week of treatment. If a patient shows no clinical improvement after four weeks of treatment with LOPROX® Topical Suspension the diagnosis should be redetermined. Patients with tinea versicolor usually exhibit clinical and mycological clearing after two weeks of treatment.

HOW SUPPLIED

LOPROX® (ciclopirox) Topical Suspension 0.77% is supplied in 30 mL bottles (NDC 99207-022-30), and 60 mL bottles (NDC 99207-022-60).

Bottle space provided to allow for vigorous shaking before each use.

Store between 5º - 25ºC (41º - 77ºF).

US Patent Pending

Manufactured for:

Medicis, The Dermatology Company

Scottsdale, AZ 85256

by: DPT Lakewood

Lakewood, NJ 08701

Prescribing Information as of 06/2013.

16100303

LOPROX® GEL

(ciclopirox) 0.77%

FOR DERMATOLOGIC USE ONLY.

NOT FOR USE IN EYES.

Rx Only

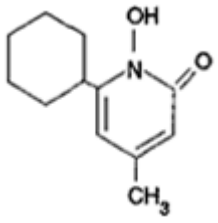
DESCRIPTION

LOPROX® Gel (ciclopirox) 0.77% contains a synthetic antifungal agent, ciclopirox. It is intended for topical dermatologic use only.

Each gram of LOPROX® Gel contains 7.70 mg of ciclopirox in a gel consisting of purified water USP, isopropyl alcohol USP, octyldodecanol NF, dimethicone copolyol 190, carbomer 980, sodium hydroxide NF, and docusate sodium USP.

LOPROX® Gel is a white, slightly fluid gel.

The chemical name for ciclopirox is 6-cyclohexyl-1-hydroxy-4-methyl-2(1*H*)-pyridinone, with the empirical formula $C_{12}H_{17}NO_2$ and a molecular weight of 207.27. The CAS Registry Number is [29342-05-0]. The chemical structure is:



CLINICAL PHARMACOLOGY

Mechanism of Action

Ciclopirox is a hydroxypyridone antifungal agent although the relevance of this property for the indication of seborrheic dermatitis is not known. Ciclopirox acts by chelation of polyvalent cations (Fe^{3+} or Al^{3+}), resulting in the inhibition of the metal-dependent enzymes that are responsible for the degradation of peroxides within the fungal cell.

Pharmacokinetics

A comparative study of the pharmacokinetics of LOPROX® Gel, and LOPROX® Cream (ciclopirox olamine) 0.77% in 18 healthy males indicated that systemic absorption of ciclopirox from LOPROX® Gel was higher than that of LOPROX® Cream. A 5 gm dose of LOPROX® Gel produced a mean (±SD) peak serum concentration of 25.02 (±20.6) ng/mL total ciclopirox and 5 gm of LOPROX® Cream produced 18.62 (±13.56) ng/mL

total ciclopirox. Approximately 3% of the applied ciclopirox was excreted in the urine within 48 hours after application, with a renal elimination half-life of about 5.5 hours.

In a study of LOPROX® Gel, 16 men with moderate to severe tinea cruris applied approximately 15 grams/day of the gel for 14.5 days. The mean (±SD) dose-normalized values of C_{max} for total ciclopirox in serum were 100 (±42) ng/mL on Day 1 and 238 (±144) ng/mL on Day 15. During the 10 hours after dosing on Day 1, approximately 10% of the administered dose was excreted in the urine.

Microbiology

Ciclopirox is a hydroxypyridinone antifungal agent that inhibits the growth of pathogenic dermatophytes. Ciclopirox has been shown to be active against most strains of the following microorganisms both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section:

Trichophyton rubrum, Trichophyton mentagrophytes, and Epidermophyton floccosum

INDICATIONS AND USAGE

Superficial Dermatophyte Infections

LOPROX® Gel is indicated for the topical treatment of interdigital tinea pedis and tinea corporis due to *Trichophyton rubrum, Trichophyton mentagrophytes,* or *Epidermophyton floccosum.*

Seborrheic Dermatitis

LOPROX® Gel is indicated for the topical treatment of seborrheic dermatitis of the scalp.

CONTRAINDICATIONS

LOPROX® Gel is contraindicated in individuals who have shown hypersensitivity to any of its components.

WARNINGS

LOPROX® Gel is not for ophthalmic, oral, or intravaginal use.

Keep out of reach of children.

PRECAUTIONS

If a reaction suggesting sensitivity or chemical irritation should occur with the use of LOPROX® Gel, treatment should be discontinued and appropriate therapy instituted. A transient burning sensation may occur, especially after application to sensitive areas. Avoid contact with eyes. Efficacy of LOPROX® Gel in immunosuppressed individuals has not been studied. Seborrheic dermatitis in association with acne, atopic dermatitis, Parkinsonism, psoriasis and rosacea has not been studied with LOPROX® Gel. Efficacy in the treatment of plantar and vesicular types of tinea pedis has not been established.

Information for Patients

The patient should be told the following:

1. Use LOPROX® Gel as directed by the physician. Avoid contact with the eyes and mucous membranes. LOPROX® Gel is for external use only.
2. Use the medication for fungal infections for the full treatment time even though symptoms may have improved, and notify the physician if there is no improvement after 4 weeks.
3. A transient burning/stinging sensation may be felt. This may occur in approximately 15% to 20% of cases, when LOPROX® Gel is used to treat seborrheic dermatitis of the scalp.
4. Inform the physician if the area of application shows signs of increased irritation or possible sensitization (redness with itching, burning, blistering, swelling, and/or oozing).
5. Avoid the use of occlusive dressings.
6. Do not use this medication for any disorder other than that for which it is prescribed.

Carcinogenesis, Mutagenesis, Impairment of Fertility

A 104-week dermal carcinogenicity study in mice was conducted with ciclopirox cream formulation applied at doses up to 1.93% (100 mg/kg/day or 300 mg/m^2/day). No increase in drug related neopalsms was noted when compared to control.

The following in vitro genotoxicity tests have been conducted with ciclopirox: evaluation of gene mutation in the Ames Salmonella and E. coli assays (negative); chromosome aberration assays in V79 Chinese hamster lung fibroblast cells, with and without metabolic activation (positive); chromosome aberration assays in V79 Chinese hamster lung fibroblast cells in the presence of supplemental Fe^{3+}, with and without metabolic activation (negative); gene mutation assays in the HGPRT-test with V79 Chinese hamster lung fibroblast cells (negative); and a primary DNA damage assay (i.e., unscheduled DNA synthesis assay in A549 human cells) (negative). An in vitro cell transformation assay in BALB/c 3T3 cells was negative for cell transformation. In an in vivo Chinese hamster bone marrow cytogenetic assay, ciclopirox was negative for chromosome aberrations at a dosage of 5000 mg/kg body weight.

A combined oral fertility and embryofetal developmental study was conducted in rats with ciclopirox olamine. No effect on fertility or reproductive performance was noted at the highest dose tested of 3.85 mg/kg/day ciclopirox (approximately 1.2 times the maximum recommended human dose based on body surface area comparisons).

Pregnancy

Teratogenic effects: Pregnancy Category B

There are no adequate or well-controlled studies in pregnant women. Therefore, LOPROX Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Oral embryofetal developmental studies were conducted in mice, rats, rabbits and monkeys. Ciclopirox or ciclopirox olamine was orally administered during the period of organogenesis. No maternal toxicity, embryotoxicity or teratogenicity were noted at the highest doses of 77, 125, 80 and 38.5 mg/kg/day ciclopirox in mice, rats, rabbits and monkeys, respectively (approximately 11, 37, 51 and 24 times the maximum recommended human dose based on body surface area comparisons, respectively).

Dermal embryofetal developmental studies were conducted in rats and rabbits with ciclopirox olamine dissolved in PEG 400. Ciclopirox olamine was topically administered during the period of organogenesis. No maternal toxicity, embryotoxicity or teratogenicity were noted at the highest doses of 92 mg/kg/day and 77 mg/kg/day ciclopirox in rats and rabbits, respectively (approximately 27 and 49 times the maximum recommended human dose based on body surface area comparisons, respectively).

Nursing Mothers

It is not known whether this drug is excreted in human milk. Since many drugs are excreted in human milk, caution should be exercised when LOPROX® Gel is administered to a nursing woman.

Pediatric Use

The efficacy and safety of LOPROX® Gel in pediatric patients below the age of 16 years have not been established.

ADVERSE REACTIONS

In clinical trials, 140 (39%) of 359 subjects treated with LOPROX® Gel reported adverse experiences, irrespective of relationship to test materials, which resulted in 8 subjects discontinuing treatment. The most frequent experience reported was skin burning sensation upon application, which occurred in approximately 34% of seborrheic dermatitis patients and 7% of tinea pedis patients. Adverse experiences occurring between 1% to 5% were contact dermatitis and pruritus. Other reactions that occurred in less than 1% included dry skin, acne, rash, alopecia, pain upon application, eye pain, and facial edema.

DOSAGE AND ADMINISTRATION

Superficial Dermatophyte Infections

Gently massage LOPROX® Gel into the affected areas and surrounding skin twice daily, in the morning and evening immediately after cleaning or washing the areas to be treated. Interdigital tinea pedis and tinea corporis should be treated for 4 weeks. If a patient shows no clinical improvement after 4 weeks of treatment, the diagnosis should be reviewed.

Seborrheic Dermatitis of the Scalp

Apply LOPROX® Gel to affected scalp areas twice daily, in the morning and evening for 4 weeks. Clinical improvement usually occurs within the first week with continuing resolution of signs and symptoms through the fourth week of treatment. If a patient shows no clinical improvement after 4 weeks of treatment, the diagnosis should be reviewed.

HOW SUPPLIED

LOPROX® Gel (ciclopirox) 0.77% is supplied in 30 g tubes (NDC 99207-013-30), 45 g tubes (NDC 99207-013-45), and 100 g tubes (NDC 99207-013-01).

Store at 15°-30°C (59°-86°F).

Prescribing Information as of 06/2013

Manufactured for:

Medicis, The Dermatology Company

Scottsdale, AZ 85256

by: Contract Pharmaceuticals Limited

Mississauga, Ontario Canada L5N 6L6

U.S. Patents 7,018,656 and 7,026,337

LOPROX is a registered trademark of Medicis Pharmaceutical Corporation.

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