

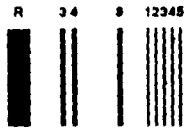
**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75-581

APPROVED DRAFT LABELING

8054



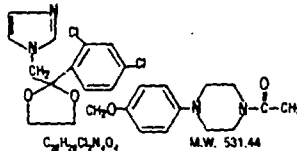
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KETOCONAZOLE CREAM

DESCRIPTION

Ketoconazole Cream, 2% contains the broad-spectrum synthetic antifungal agent, ketoconazole 2%. Each gram, for topical administration, contains ketoconazole 20 mg and is formulated in an aqueous cream vehicle consisting of propylene glycol, purified water, cetyl alcohol, isopropyl myristate, sorbitan monostearate, polysorbate 80, polysorbate 80, and sodium sulfite, anhydrous.

Ketoconazole is cis-1-acetyl-4-[[2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazine and has the following structural formula:



CLINICAL PHARMACOLOGY

When ketoconazole cream, 2% was applied dermally to intact or abraded skin of Beagle dogs for 28 consecutive days at a dose of 80 mg, there were no detectable plasma levels using an assay method having a lower detection limit of 2 ng/ml.

After a single topical application to the chest, back and arms of normal volunteers, systemic absorption of ketoconazole was not detected at the 5 ng/ml level in blood over a 72-hour period.

Two dermal irritation studies, a human sensitization test, a phototoxicity study and a photoallergy study conducted in 38 male and 62 female volunteers showed no contact sensitization of the delayed hypersensitivity type, no irritation, no phototoxicity and no photoallergic potential due to ketoconazole cream, 2%.

Microbiology: Ketoconazole is a broad spectrum synthetic antifungal agent which inhibits the *in vitro* growth of the following common dermatophytes and yeasts by altering the permeability of the cell membrane: dermatophytes: *Trichophyton rubrum*, *T. mentagrophytes*, *T. tonsurans*, *Microporum canis*, *M. audouinii*, *M. gypseum* and *Epidermophyton floccosum*; yeasts: *Candida albicans*, *Malassezia ovale* (*Phytoporum ovale*) and *C. tropicalis*; and the organisms responsible for tinea versicolor, *Malassezia furfur* (*Phytoporum orbiculare*). Only those organisms listed in the INDICATIONS AND USAGE Section have been proven to be clinically affected. Development of resistance to ketoconazole has not been reported.

Mode of Action: *In vitro* studies suggest that ketoconazole impairs the synthesis of ergosterol, which is a vital component of fungal cell membranes. It is postulated that the therapeutic effect of ketoconazole in seborrheic dermatitis is due to the reduction of *M. ovale*, but this has not been proven.

INDICATIONS AND USAGE

Ketoconazole Cream, 2% is indicated for the topical treatment of tinea corporis, tinea cruris and tinea pedis caused by *Trichophyton rubrum*, *T. mentagrophytes* and *Epidermophyton floccosum*; in the treatment of tinea (pityriasis) versicolor caused by *Malassezia furfur* (*Phytoporum orbiculare*); in the treatment of cutaneous candidiasis caused by *Candida* spp. and in the treatment of seborrheic dermatitis.

CONTRAINDICATIONS

Ketoconazole Cream, 2% is contraindicated in persons who have shown hypersensitivity to the active or excipient ingredients of this formulation.

WARNINGS

Ketoconazole Cream, 2% is not for ophthalmic use.

Ketoconazole Cream, 2% contains sodium sulfite anhydrous, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

PRECAUTIONS

General: If a reaction suggesting sensitivity or chemical irritation should occur, use of the medication should be discontinued. Hepatitis (1:10,000 reported incidence) and, at high doses, lowered testosterone and ACTH induced corticosteroid serum levels have been seen with orally administered ketoconazole; these effects have not been seen with topical ketoconazole.

Carcinogenesis, Mutagenesis, Impairment of Fertility: A long-term feeding study in Swiss Albino mice and in Wistar rats showed no evidence of oncogenic activity. The dominant lethal mutation test in male and female mice revealed that single oral doses of ketoconazole as high as 80 mg/kg produced no mutation in any stage of germ cell development. The Ames' Salmonella microsomal activator assay was also negative.

Pregnancy: *Teratogenic effects:* **Pregnancy Category C:** Ketoconazole has been shown to be teratogenic (syndactyly and oligodactyly) in the rat when given orally in the diet at 80 mg/kg/day, (10 times the maximum recommended human oral dose). However, these effects may be related to maternal toxicity, which was seen at this and higher dose levels.

There are no adequate and well-controlled studies in pregnant women. Ketoconazole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether ketoconazole cream, 2% administered topically could result in sufficient systemic absorption to produce detectable quantities in breast milk. Nevertheless, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

During clinical trials 45 (5%) of 905 patients treated with ketoconazole cream, 2% and 5 (2.4%) of 208 patients treated with placebo reported side effects consisting mainly of severe irritation, pruritus and stinging. One of the patients treated with ketoconazole cream developed a painful allergic reaction.

In worldwide postmarketing experience, rare reports of contact dermatitis have been associated with ketoconazole cream or one of its excipients, namely sodium sulfite or propylene glycol.

DOSE AND ADMINISTRATION

Cutaneous candidiasis, tinea corporis, tinea cruris, tinea pedis, and tinea (pityriasis) versicolor: It is recommended that ketoconazole cream, 2% be applied once daily to cover the affected and immediate surrounding area. Clinical improvement may be seen fairly soon after treatment is begun; however, candidal infections and tinea cruris and corporis should be treated for two weeks in order to reduce the possibility of recurrence. Patients with tinea versicolor usually require two weeks of treatment. Patients with tinea pedis require six weeks of treatment.

Sabornhic dermatitis: Ketoconazole Cream, 2% should be applied to the affected area twice daily for four weeks or until clinical clearing.

If a patient shows no clinical improvement after the treatment period, the diagnosis should be redetermined.

HOW SUPPLIED

Ketoconazole Cream, 2% is supplied in 15, 30, and 60 gram tubes.

Store below 25°C (77°F)

Manufactured By:
TEVA PHARMACEUTICALS USA
Sellersville, PA 19380

Printed in USA
Iss. 8/99
119841

NDC 0093-0840-92

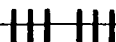
KETOCONAZOLE CREAM

2%
Rx only

60 GRAMS

TEVA

For dermatologic use only



How to Use: For information for use see accompanying product literature.

Store below 25°C (77°F).

Warning: Not for ophthalmic use. Keep this and all medications out of the reach of children.

TEVA PHARMACEUTICALS USA, Sellersville, PA 18960

Mat. No. C19839

NDC 0093-0840-92

KETOCONAZOLE CREAM

2%
Rx only

60 GRAMS

TEVA

For dermatologic use only

Each gram contains: ketoconazole 20 mg, propylene glycol, purified water, cetyl alcohol, stearyl alcohol, isopropyl myristate, sorbitan monostearate, polysorbate 60, polysorbate 80, and sodium sulfite, anhydrous.

See crimp end of tube for control number and expiration date.



0093-0840-92



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Mat. No. C19839

KETOCONAZOLE
CREAM
2%
60 GRAMS

PC Inst. 899

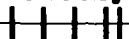
NDC 0093-0840-30

KETOCONAZOLE CREAM

2%

Rx only

For dermatologic use only



30 GRAMS

TEVA

Mkt. No. C19837

Usual Dosage: For information for use see accompanying product literature.

Store below 25°C (77°F).

Warning: Not for ophthalmic use. Keep this and all medications out of the reach of children.

TEVA PHARMACEUTICALS USA, Sellersville, PA 18960

NDC 0093-0840-30

KETOCONAZOLE CREAM

2%

Rx only

For dermatologic use only

30 GRAMS

TEVA

KETOCONAZOLE
CREAM
2%
30 GRAMS

P.C. Iss. 8/99

Mkt. No. C19837

Each gram contains: ketoconazole 20 mg, propylene glycol, purified water, cetyl alcohol, stearyl alcohol, isopropyl myristate, sorbitan monostearate, polysorbate 60, polysorbate 80, and sodium sulfite, anhydrous
See crimp end of tube for control number and expiration date.



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NDC 0093-0840-30

KETOCONAZOLE CREAM

2%

Rx only

For dermatologic use only



30 GRAMS

TEVA

Mkt. No. C19837

Usual Dosage: For information for use see accompanying product literature.

Store below ~~25°C (77°F)~~

Warning: Not for ophthalmic use. Keep this and all medications out of the reach of children.

TEVA PHARMACEUTICALS USA, Sellersville, PA 18960

NDC 0093-0840-30

KETOCONAZOLE CREAM

2%

Rx only

For dermatologic use only

30 GRAMS

TEVA

PC No. 8789

30 grams

KETOCONAZOLE
CREAM
2%

Mkt. No. C19837

Each gram contains: ketoconazole 20 mg, propylene glycol, purified water, cetyl alcohol, stearyl alcohol, isopropyl myristate, sorbitan monostearate, polysorbate 60, polysorbate 80, and sodium sulfite, anhydrous.

See crimp end of tube for control number and expiration date.



0093-0840-30



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NDC 0093-0840-15

KETOCONAZOLE CREAM

2%

Rx only

For dermatologic use only

15 GRAMS

TEVA



Usual Dosage: For information for use see accompanying product literature.

Store below 25°C (77°F).

Warning: Not for ophthalmic use. Keep this and all medications out of the reach of children.

TEVA PHARMACEUTICALS USA, Sellersville, PA 18960

MAT. NO. C19835

PC (see USP)

15 grams /

2%
CREAM

KETOCONAZOLE

NDC 0093-0840-15

KETOCONAZOLE CREAM

2%

Rx only

For dermatologic use only

15 GRAMS

TEVA

Each gram contains: ketoconazole 20 mg; propylene glycol, purified water, cetyl alcohol, stearyl alcohol, isopropyl myristate, sorbitan monostearate, polysorbate 60, polysorbate 80, and sodium sulfite, anhydrous.

See package insert for control number and expiration date.

MAT. NO. C19835



0093-0840-15



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ANDA #75-581
KETOCONAZOLE CREAM, 2%
60 gram Tube

NDC 0093-0840-92 -

KETOCONAZOLE CREAM
2%
Rx only



For dermatologic use only

Usual Dosage: For information for use see accompanying product literature.

Store below 25°C (77°F).

Warning: Not for ophthalmic use. Keep this and all medications out of the reach of children.

See crimp end of tube for control number and expiration date.

Each gram contains: ketoconazole 20 mg, propylene glycol, purified water, cetyl alcohol, stearyl alcohol, isopropyl myristate, sorbitan monostearate, polysorbate 60, polysorbate 80, and sodium sulfite, anhydrous.

TEVA PHARMACEUTICALS USA, Sellersville, PA 18960

C19840
Iss. 8/99



NDC 0093-0840-92 .

KETOCONAZOLE CREAM
2%
Rx only



For dermatologic use only

Usual Dosage: For information for use see accompanying product literature.

Store below 25°C (77°F).

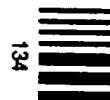
Warning: Not for ophthalmic use. Keep this and all medications out of the reach of children.

See crimp end of tube for control number and expiration date.

Each gram contains: ketoconazole 20 mg, propylene glycol, purified water, cetyl alcohol, stearyl alcohol, isopropyl myristate, sorbitan monostearate, polysorbate 60, polysorbate 80, and sodium sulfite, anhydrous.

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ANDA #75-581
KETOCONAZOLE CREAM, 2%
30 gram Tube

NDC 0093-0840-30

KETOCONAZOLE CREAM
2%
Rx only

30 GRAMS

TEVA

For dermatologic use only

Usual Dosage: For information for use see accompanying product literature.

Store below 25°C (77°F).

Warning: Not for ophthalmic use. Keep this and all medications out of the reach of children.

See crimp end of tube for control number and expiration date.

Each gram contains: ketoconazole 20 mg, propylene glycol, purified water, cetyl alcohol, stearyl alcohol, isopropyl myristate, sorbitan monostearate, polysorbate 60, polysorbate 80, and sodium sulfite, anhydrous.

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TEVA PHARMACEUTICALS USA, Sellersville, PA 18960

C19838
Iss. 8/99

NDC 0093-0840-30

KETOCONAZOLE CREAM
2%
Rx only

30 GRAMS

TEVA

For dermatologic use only

Usual Dosage: For information for use see accompanying product literature.

Store below 25°C (77°F).

Warning: Not for ophthalmic use. Keep this and all medications out of the reach of children.

See crimp end of tube for control number and expiration date.

Each gram contains: ketoconazole 20 mg, propylene glycol, purified water, cetyl alcohol, stearyl alcohol, isopropyl myristate, sorbitan monostearate, polysorbate 60, polysorbate 80, and sodium sulfite, anhydrous.

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TEVA PHARMACEUTICALS USA, Sellersville, PA 18960

C19838
Iss. 8/99

ANDA #75-581
KETOCONAZOLE CREAM, 2%
15 gram Tube

NDC 0093-0840-15

KETOCONAZOLE CREAM 15 GRAMS
2%
Rx only **TEVA**

For dermatologic use only

Usual Dosage: For information for use see accompanying product literature.
Store below 25°C (77°F).

Warning: Not for ophthalmic use. Keep this and all medications out of the reach of children.

See crimp end of tube for control number and expiration date.

Each gram contains: ketoconazole 20 mg, propylene glycol, purified water, cetyl alcohol, stearyl alcohol, isopropyl myristate, sorbitan monostearate, polysorbate 60, polysorbate 80, and sodium sulfite, anhydrous.

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C19636
Iss. 8/99



NDC 0093-0840-15

KETOCONAZOLE CREAM 15 GRAMS
2%
Rx only **TEVA**

For dermatologic use only

Usual Dosage: For information for use see accompanying product literature.
Store below 25°C (77°F).

Warning: Not for ophthalmic use. Keep this and all medications out of the reach of children.

See crimp end of tube for control number and expiration date.

Each gram contains: ketoconazole 20 mg, propylene glycol, purified water, cetyl alcohol, stearyl alcohol, isopropyl myristate, sorbitan monostearate, polysorbate 60, polysorbate 80, and sodium sulfite, anhydrous.

TEVA PHARMACEUTICALS USA Sellersville PA 18960

C19636
Iss. 8/99

