HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use XOLEGEL Gel safely and effectively. See full prescribing information for XOLEGEL Gel.

XOLEGEL® (ketoconazole) Gel 2%
For Topical Use
Initial U.S. Approval: 1981

----------INDICATIONS AND USAGE----------

- XOLEGEL is an azole antifungal indicated for topical treatment of seborrheic dermatitis in immunocompetent adults and children 12 years of age and older. (1, 12.1)
- Safety and efficacy of XOLEGEL for treatment of fungal infections have not been established. (1)

----------DOSAGE AND ADMINISTRATION----------

- XOLEGEL is for topical use only, and not for oral, ophthalmic, or intravaginal use. (2)
- XOLEGEL should be applied once daily to the affected area for 2 weeks. (2)

----------DOSAGE FORMS AND STRENGTHS----------
XOLEGEL is a translucent to clear amber colored gel containing 2% ketoconazole. (3)

----------CONTRAINDICATIONS----------
None.

----------WARNINGS AND PRECAUTIONS----------

XOLEGEL is flammable. Avoid using near fire, flame, or smoking during and immediately following application of XOLEGEL. (5.1)

----------ADVERSE REACTIONS----------

- The most common treatment-related adverse reaction was application site burning (4%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Stiefel Laboratories, Inc. at 1-866-440-5508 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 11/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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3 DOSAGE FORMS AND STRENGTHS

XOLEGEL is a translucent to clear amber colored gel containing 2% ketoconazole.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Flammable Contents

XOLEGEL is flammable. Avoid being near fire, flame, or smoking during and immediately following application of XOLEGEL.

5.2 Systemic Effects

Hepatitis 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 topically administered ketoconazole.

5.3 Local Effects

XOLEGEL can cause local irritation at the application site. If irritation occurs or if the disease worsens, use of the medication should be discontinued and the health care provider should be contacted *[see ADVERSE REACTIONS (6.1)]*.

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In the 3 safety and efficacy trials, 65 of 933 subjects (7%) experienced at least one treatment-related adverse event. The most common treatment-related adverse reaction was application site burning (4%). Treatment-related application site reactions that were reported in < 1% of subjects were: dermatitis, discharge, dryness, erythema, irritation, pain, pruritus, and pustules. Other treatment-related adverse reactions that were reported in < 1% of subjects were: eye irritation, eye swelling, keratoconjunctivitis sicca, impetigo, pyogenic granuloma, dizziness, headache, paresthesia, acne, nail discoloration, facial swelling.

6.2 Post-marketing Experience

Adverse events identified during post approval use of XOLEGEL include burning sensation, pain, skin irritation, and erythema. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

7 DRUG INTERACTIONS

Formal drug interaction studies with XOLEGEL have not been performed. Coadministration of oral ketoconazole with CYP3A4 metabolized HMG-CoA reductase inhibitors such as simvastatin, lovastatin and atorvastatin, may increase the risk of skeletal muscle toxicity, including rhabdomyolysis. These effects have not been observed with topically administered ketoconazole.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C:

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

Reproductive toxicity studies have not been performed with XOLEGEL. Ketoconazole was tested for its effects on offspring in the rat at oral doses of 10, 20, 40, 80, and 160 mg/kg. Ketoconazole was teratogenic (syndactylia and oligodactylia) at 80 mg/kg/day and embryotoxic at 160 mg/kg/day (76 and 152 times the human dose, respectively). However, these effects may be related to maternal toxicity, which was also seen at these dose levels.

Oral doses of 10, 20, 40, 80, and 160 mg/kg were studied in pre- and postnatal development studies in rats. Doses of 40 mg/kg (38 times the human dose) and above were associated with maternal toxicity, an increase in the length of gestation, and an increase in the number of stillborn fetuses. These doses of ketoconazole were also toxic to the offspring, resulting in a decrease in fetal/pup weights and viability.

8.3 Nursing Mothers

It is not known whether XOLEGEL is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when XOLEGEL is administered to a nursing woman.

If used during lactation and XOLEGEL is applied to the chest, care should be taken to avoid accidental ingestion by the infant.

8.4 Pediatric Use

Safety and effectiveness in pediatric subjects below the age of 12 have not been established.

8.5 Geriatric Use

Of the 933 subjects in the three safety and efficacy trials, 193 (20.7%) were 65 and older, while 61 (6.5%) were 75 and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects but greater sensitivity of some older individuals cannot be ruled out.

10 OVERDOSAGE

XOLEGEL is intended for topical use only.

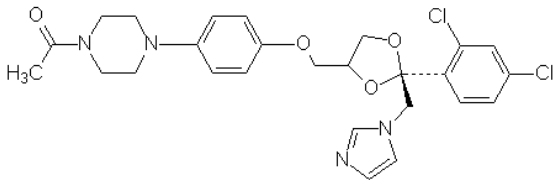
There has been no experience of overdose with XOLEGEL. No incidents of accidental ingestion have been reported. A health care provider or poison control center should be contacted in the event of accidental ingestion.

11 DESCRIPTION

XOLEGEL contains the antifungal agent ketoconazole USP at 2% in a topical anhydrous gel vehicle for topical administration.

Chemically, ketoconazole is (±)-cis-1-Acetyl-4-[p-[[2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazine, with the molecular formula $C_{26}H_{28}Cl_2N_4O_4$ and a molecular weight of 531.43.

Figure 1



Each gram contains: 20 mg ketoconazole USP, dehydrated alcohol (34%), ascorbic acid, butylated hydroxytoluene, citric acid monohydrate, glycerin, hydroxypropyl cellulose, polyethylene glycol 400, PPG-15 stearyl ether, propylene glycol, FD&C yellow No. 6, and FD&C yellow No. 10.

XOLEGEL is a smooth, translucent to clear, amber gel.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of ketoconazole in the treatment of seborrheic dermatitis is unknown.

12.2 Pharmacodynamics

Pharmacodynamic markers for seborrheic dermatitis have not been identified.

12.3 Pharmacokinetics

In a pharmacokinetic absorption trial, eighteen subjects, both males and females, with severe seborrheic dermatitis (range 1-14% of body surface area) applied XOLEGEL once daily for 2 weeks. The median total amount of gel applied was 4.6 g (range 1.65–46.3 g). Daily doses ranged from 0.05 to 3.47 g. Mean (± standard deviation [SD]) peak plasma levels were 1.35 (± 3.18) ng/mL on Day 7 (range from <0.1 ng/mL, to 13.9 ng/mL), and 0.80 (± 1.22) ng/mL on Day 14 (range from <0.1 ng/mL to 5.4 ng/mL). Median T_{max} was 8 hours on Day 7 and 7 hours on Day 14. Mean (± SD) AUC_{0-24} values were 20.8 (± 44.7) ng·h/mL and 15.6 (± 26.4) ng·h/mL on Day 7 and 14, respectively.

The plasma levels from an oral dose of 200 mg ketoconazole taken with a meal are approximately 250 times higher than the resulting plasma levels of ketoconazole following topical application of XOLEGEL.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies to assess the carcinogenic potential of XOLEGEL have not been conducted. A long-term feeding study in Swiss Albino mice and in Wistar rats showed no evidence of oncogenic activity. Ketoconazole gel at a dosage up to 5 mg/kg/dose is not photocarcinogenic when topically applied to hairless mice five days per week for a period of 40 weeks. Ketoconazole produced no evidence of mutagenicity in the dominant lethal mutation test in male and female mice at single oral doses up to 80 mg/kg. When tested in the Ames assay, ketoconazole was found to be non-mutagenic to *Salmonella typhimurium* in the presence and absence of metabolic activation. Ketoconazole, in combination with another drug, gave equivocal results in the mouse micronucleus test. At oral doses of 75 to 80 mg/kg/day (71 to 76 times the human dose) ketoconazole impaired the reproductive performance in female (decreased pregnancy and implantation rates) and male (increased abnormal sperm and decreased sperm motility) rats.

14 CLINICAL STUDIES

Study 1 was a multicenter, double-blind, randomized, vehicle-controlled trial which enrolled 459 subjects 12 years of age and older with moderate to severe seborrheic dermatitis. A total of 229 subjects were treated with XOLEGEL, and 230 subjects were treated with vehicle. All subjects were treated once daily for 14 days, and efficacy was assessed at Day 28 (i.e., 2 weeks after end of treatment). Effective Treatment was defined as:

- an Investigator's Global Assessment score of ≤ 1 (completely clear or almost clear) and
- erythema and scaling scores of 0 (none) if the baseline score was 2, or 1 (mild) if the baseline score was 3.

The proportion of subjects effectively treated is shown in Table 1.

Table 1: Trial Results

	XOLEGEL N=229	*Vehicle N=230*
Number and proportion of subjects effectively treated	58 (25.3%)	32 (13.9%)

Two additional double-blind, randomized, vehicle-controlled, parallel, and multi-center trials that included a total of 316 subjects treated with XOLEGEL provided supportive evidence of the efficacy of XOLEGEL for treatment of seborrheic dermatitis. Subjects applied either XOLEGEL or vehicle study treatment to the affected area(s) once daily for 14 days and were followed through Day 28. Efficacy was assessed by the proportion of subjects who were completely clear at Day 28.

The contribution to efficacy of individual components of the vehicle has not been established.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

XOLEGEL® (ketoconazole, USP) Gel, 2% is supplied in 45-gram (NDC 0145-0003-05) white-coated aluminum tubes with white caps, and is dispensed with FDA-Approved Patient Labeling. (17.2)

16.2 Storage and Handling

Store at 25°C (77°F); excursions permitted to 15° - 30°C (59° - 86°F).
Contents are flammable.
Keep out of reach of children.

17 PATIENT COUNSELING INFORMATION

[See FDA-Approved Patient Labeling (Patient Information)]

- This medication is to be used as directed by the health care provider. It is for external use only.
- XOLEGEL may be irritating to mucus membranes. Contact with the eyes, nostrils, and mouth should be avoided.
- As with any topical medication, patients should wash their hands after application.
- This medication should not be used for any disorder other than that for which it has been prescribed.
- Patients should report any signs of adverse reactions to their health care provider.

XGL: 2PI