

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-946

LABELING

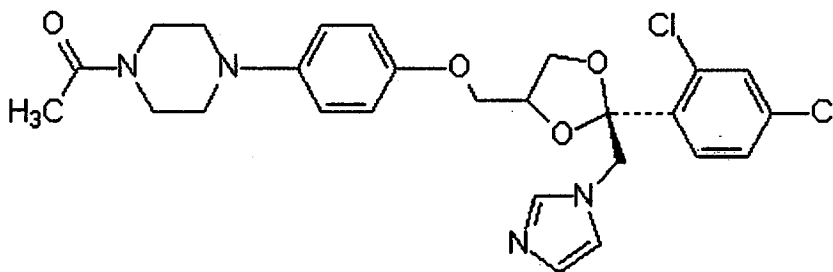
XOLEGEL (KETOCONAZOLE, USP) GEL, 2%
Rx ONLY
FOR TOPICAL USE ONLY.
NOT FOR OPHTHALMIC, ORAL OR INTRAVAGINAL USE.

DESCRIPTION

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

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 a molecular weight of 531.43.

Figure 1



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

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

CLINICAL PHARMACOLOGY

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

Pharmacokinetics:

In a pharmacokinetic absorption study, eighteen subjects, both males and females, with severe seborrheic dermatitis (range 1-14% of body surface area) applied XOLEGEL Gel

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 ($\pm$ standard deviation [SD]) peak plasma levels were 1.35 ($\pm$ 3.18) ng/mL on Day 7 (range from <0.1 ng/mL to 13.9 ng/mL), and 0.80 ($\pm$ 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 ($\pm$ SD) AUC_{0-24} values were 20.8 ($\pm$ 44.7) ng·h/mL and 15.6 ($\pm$ 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 Gel.

Microbiology: Ketoconazole is an antifungal agent which, *in vitro*, inhibits the synthesis of ergosterol, a key sterol in the cell membrane of *Malassezia furfur* (also known as *Pityrosporum ovale*), which leads to the death of the organism.

Mode of Action: It is postulated that the therapeutic effect of ketoconazole in seborrheic dermatitis is due to the reduction of *Malassezia furfur* (also known as *Pityrosporum ovale*), but this has not been proven.

CLINICAL STUDIES

Study 1 was a multicenter, double-blind, randomized, vehicle-controlled trial which enrolled 459 patients 12 years of age and older with moderate to severe seborrheic dermatitis. A total of 229 patients were treated with XOLEGEL Gel, and 230 patients were treated with vehicle. All patients 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 patients effectively treated is shown in the following table.

Table 1

	XOLEGEL Gel N=229	Vehicle Gel N=230
Proportion of patients effectively treated	58 (25.3%)	32 (13.9%)

Two additional double-blind, randomized, vehicle-controlled, parallel, and multi-center studies that included a total of 316 patients treated with XOLEGEL Gel provided supportive evidence of the efficacy of XOLEGEL Gel for treatment of seborrheic dermatitis. Patients applied either XOLEGEL Gel 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 patients who were completely clear at Day 28.

INDICATIONS AND USAGE

XOLEGEL Gel is indicated for the topical treatment of seborrheic dermatitis in immunocompetent adults and children 12 years of age and older.

Safety and efficacy of XOLEGEL Gel for treatment of fungal infections have not been established.

CONTRAINDICATIONS

XOLEGEL Gel is contraindicated in those patients with a history of sensitivity reactions to any of its components. It should be discontinued if hypersensitivity is noted.

WARNINGS

Avoid fire, flame, or smoking during and immediately following application of XOLEGEL Gel.

PRECAUTIONS

General: XOLEGEL Gel is for topical use only, and not for ophthalmic, oral or intravaginal use. If irritation occurs or if the disease worsens, use of the medication should be discontinued, and the health care provider should be contacted.

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 topical ketoconazole.

Information for Patients:

1. This medication is to be used as directed by the health care provider. It is for external use only.
2. XOLEGEL Gel may be irritating to mucous membranes. Contact with the eyes, nostrils and mouth should be avoided.
3. As with any topical medication, patients should wash their hands after application.

4. This medication should not be used for any disorder other than that for which it has been prescribed.
5. Patients should report any signs of adverse reactions to their health care provider.

Drug Interactions: Formal drug interaction studies with XOLEGEL Gel have not been performed.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies to assess the carcinogenic potential of XOLEGEL Gel 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.

Pregnancy Category C: Reproductive toxicity studies have not been performed with XOLEGEL Gel. 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.

Non-teratogenic Effects:

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.

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

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

Pediatric Use: Safety and effectiveness in pediatric patients below the age of 12 have not been established.

Geriatric Use: Of the 933 subjects in the three safety and efficacy studies, 193 (20.7%) were 65 and over, while 61 (6.5%) were 75 and over. 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.

ADVERSE REACTIONS

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 practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Overall Summary of Adverse Events Reported by >1% of Subjects

Table 2

Adverse Event	XOLEGEL Gel N=545 N (%)	Gel Vehicle N=388 N (%)
Any Adverse Event	89 (16.3)	67 (17.3)
Application site burning	23 (4.2)	12 (3.1)
Headache	6 (1.1)	3 (0.8)

NOTE: The same adverse event recorded by a subject at different visits count as one event for that subject, and the strongest intensity and relationship to treatment is used. At each level of summarization (System Organ Class and Preferred Term) subjects are only counted once.

In the three safety and efficacy studies, 65 of 933 subjects (7%) experienced at least one treatment-related adverse event. The most common treatment-related adverse event was application site burning (see Table 2). 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.

Contact sensitization, cumulative irritation, phototoxicity and photoallergy studies were conducted with XOLEGEL Gel. Under the conditions of study, XOLEGEL Gel did not demonstrate contact sensitization, phototoxicity or photoallergenicity, but did demonstrate potential to cause irritation.

OVERDOSAGE

XOLEGEL Gel is intended for topical use only.

There has been no experience of overdose with XOLEGEL Gel. 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.

DOSAGE AND ADMINISTRATION

XOLEGEL Gel should be applied once daily to the affected area for 2 weeks.

HOW SUPPLIED

XOLEGEL (ketoconazole, USP) Gel, 2% is supplied in the following size tubes:

2-gram sample tube (NDC 13478-003-02)

15-gram aluminum tube (NDC 13478-003-01)

STORAGE CONDITIONS

Store at 25°C (77°F); excursions permitted to 15° - 30°C (59° - 86°F)

Keep out of reach of children.

MANUFACTURED BY

DPT Laboratories, Ltd.
307 E. Josephine Street
San Antonio, TX 78215

FOR

Barrier Therapeutics, Inc.
600 College Road East
Princeton, NJ 08540-6697
www.barriertherapeutics.com
1-866-440-5508

US Patent Numbers: 09/562,376 and 10/722,134 (Patents Pending)

July 2006

XO-005

(Proposed Patient Leaflet)
Patient Information

XOLEGEL
(Ketoconazole, USP) Gel, 2%

Read the Patient Information that comes with XOLEGEL Gel carefully before you start using it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your health care provider. If you have any questions about XOLEGEL Gel, ask your health care provider.

XOLEGEL Gel is a prescription medicine used on the skin (topical) to treat a condition called seborrheic dermatitis. Patients with seborrheic dermatitis can have areas of dry, flaky skin (scales) on the scalp, face, ears, chest, or upper back.

XOLEGEL Gel has not been studied in children below the age of 12.

What should I tell my health care provider before using XOLEGEL Gel?

- **Tell your health care provider about all of your medical conditions, including if you are**
 - **pregnant or planning to become pregnant.** It is not known if XOLEGEL Gel can harm your unborn baby. XOLEGEL Gel should be used during pregnancy only if needed.
 - It is not known if XOLEGEL Gel passes into your breast milk or if it can harm your baby.
- **Tell your health care provider about all of the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.** It is not known if XOLEGEL Gel and other medicines can affect each other.

Know the medicines you take. Keep a list of your medicines and show it to your health care provider and pharmacist when you get a new medicine.

How should I use XOLEGEL Gel?

- **Use XOLEGEL Gel exactly as prescribed.** Talk to your health care provider if your condition gets worse or does not get better by the end of your treatment.
- **Stay away from fire, flame, or smoking while you are applying XOLEGEL Gel and right after you apply it.**
- **Wash your hands before and after applying XOLEGEL Gel.**

- Spread a thin layer of XOLEGEL Gel evenly on the affected skin with your fingertips. Be sure to cover all affected areas and the healthy skin right around the affected area.
- Do not wash the areas where you applied XOLEGEL Gel for at least three hours after you apply it.
- Wait at least 20 minutes after you spread XOLEGEL Gel on your skin before you put makeup or sunscreens on the affected areas.
- Use XOLEGEL Gel once daily for two weeks. Your skin may remain improved after you stop using XOLEGEL Gel.

What should I avoid while using XOLEGEL Gel?

- Stay away from fire, flame, or smoking while you are applying XOLEGEL Gel and right after you apply it.
- Do not touch your eyes or nose while you are applying XOLEGEL Gel. Wash your hands well after you apply it. Irritation may occur if you get XOLEGEL Gel in your eyes or nose.

What are the possible side effects of XOLEGEL Gel?

- Stop using XOLEGEL Gel and talk to your health care provider if you have itching and a rash.
- The most common side effect is a burning feeling where XOLEGEL Gel is applied.

These are not all of the side effects of XOLEGEL Gel. For more information, ask your health care provider or pharmacist.

How should I store XOLEGEL Gel?

- Store XOLEGEL Gel at 59°F to 86°F (15° to 30°C).
- Keep XOLEGEL Gel and all medicines out of the reach of children.

General information about XOLEGEL Gel

Medicines are sometimes prescribed for conditions that are not mentioned in Patient Information leaflets. Do not use XOLEGEL Gel for a condition for which it was not prescribed. Do not give XOLEGEL Gel to other people, even if they have the same symptoms that you have. It may harm them.

This Patient Information leaflet summarizes the most important information about XOLEGEL Gel. If you would like more information, talk with your health care provider. You can ask your pharmacist or health care provider for information about XOLEGEL Gel that is written for health professionals. For additional information on XOLEGEL Gel visit www.XOLEGEL.com or call Barrier Therapeutics, Inc. customer service at 1-866-440-5508.

What are the ingredients in XOLEGEL Gel?

Active ingredient: ketoconazole

Inactive ingredients: dehydrated alcohol USP, ascorbic acid USP, butylated hydroxytoluene NF, citric acid monohydrate USP, glycerin USP, hydroxypropyl cellulose NF, polyethylene glycol 400 NF, PPG-15 stearyl ether, propylene glycol USP, FD&C yellow No. 6, D&C Yellow No. 10.