

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
For Topical Use Only
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 Aqua Pharmaceuticals, LLC at 1-866-665-2782 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

Revised: 01/2011

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

FULL PRESCRIBING INFORMATION**1 INDICATIONS AND USAGE**

XOLEGEL 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 for treatment of fungal infections have not been established.

2 DOSAGE AND ADMINISTRATION

XOLEGEL is for topical use only, and not for oral, ophthalmic, or intravaginal use.

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

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 Experiences**

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 with 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.

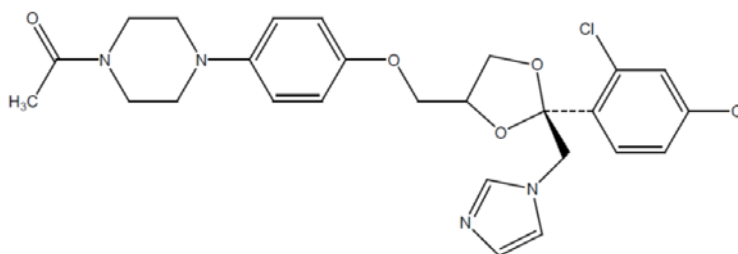
There has been no experience of overdose with XOLEGEL. No incidents of accidental ingestion have been reported. A health care provider or poison control center should be contacted in the event of accidental ingestion.

11 DESCRIPTION

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

Chemically, ketoconazole is (\pm)-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 (\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.

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

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

Two additional double-blind, randomized, vehicle-controlled, parallel, and multicenter 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) Gel, 2% is supplied in 45-gram (NDC 16110-080-45) 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.

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PATIENT INFORMATION

XOLEGEL® (Xol-a-gel)

(ketoconazole) Gel, 2%

Read the Patient Information that comes with XOLEGEL 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, ask your health care provider.

What is XOLEGEL?

XOLEGEL is a prescription medicine used on the skin to treat a skin condition called seborrheic dermatitis.

Patients with seborrheic dermatitis can have areas of dry, flaky skin on the scalp, face, ears, chest, or upper back. XOLEGEL is only to be used in adults and in children older than 12 years of age who have a normal (healthy) immune system. XOLEGEL has not been studied in children below the age of 12.

It is not known whether XOLEGEL can be used to treat fungal infections.

XOLEGEL is a translucent to clear, amber colored gel.

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

- Tell your health care provider about all of your medical conditions, including if you are pregnant or planning to become pregnant, or are breastfeeding or planning to breastfeed. XOLEGEL should be used during pregnancy and breastfeeding only if needed.
- Tell your health care provider about all of the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Keep a list of your medicines and show it to your health care provider and pharmacist. Tell your health care provider and pharmacist when you get a new medicine. It is not known if XOLEGEL and other medicines can interact with each other.

How should I use XOLEGEL?

- Use XOLEGEL 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.
- Wash your hands before and after applying XOLEGEL.
- Spread a thin layer of XOLEGEL evenly on the affected skin with your fingertips. Be sure to cover all affected areas.
- Do not wash the areas where you applied XOLEGEL for at least 3 hours after you apply it.
- Wait at least 20 minutes after you spread XOLEGEL on your skin before you put makeup or sunscreens on the affected areas.
- Use XOLEGEL once daily for 2 weeks.

What should I avoid while using XOLEGEL?

- XOLEGEL is only to be used on the skin. It is not for eye, mouth, or vaginal use.
- Do not touch your eyes, nose, or mouth while you are applying XOLEGEL. Wash your hands well after you apply it. Irritation may occur if you get XOLEGEL in your eyes, nose, or mouth.
- If used during breastfeeding and XOLEGEL is applied on the chest, take care to avoid accidental ingestion of XOLEGEL by the baby.
- XOLEGEL is flammable (it can catch fire). Stay away from heat, flame, or smoking while you are applying XOLEGEL and right after you apply it.

- This medication should not be used for any disorder other than that for which it has been prescribed.

What are the possible side effects of XOLEGEL?

- The effects of XOLEGEL during pregnancy, including whether XOLEGEL can harm your unborn baby, are not known.
- It is not known if XOLEGEL can pass into your breastmilk or if it can harm your breastfed baby.
- Stop using XOLEGEL and talk to your health care provider if you develop itching, a rash, or any skin irritation after using XOLEGEL.
- Stop using XOLEGEL and talk to your health care provider if your skin condition (seborrheic dermatitis) gets worse.
- The most common side effect is a burning feeling where XOLEGEL is applied.
- Report any side effects to your health care provider to receive immediate medical attention. You can also report suspected side effects by calling the US Food and Drug Administration at 1-800-FDA-1088, or reporting via the internet at www.fda.gov/medwatch.

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

How should I store XOLEGEL?

- Store XOLEGEL at 59°F to 86°F (15° to 30°C).
- Keep XOLEGEL and all medicines out of the reach of children.
- Contents are flammable. Avoid storing XOLEGEL near heat or flame.

General information about XOLEGEL

Medicines are sometimes prescribed for conditions that are not mentioned in Patient Information leaflets. Do not use XOLEGEL for a condition for which it was not prescribed. Do not give XOLEGEL 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. If you would like more information, talk with your health care provider. You can also ask your pharmacist or health care provider for information about XOLEGEL that is written for health professionals.

What are the ingredients in XOLEGEL?

Active ingredient: ketoconazole, USP

Inactive ingredients: dehydrated alcohol, 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.

This Patient Information leaflet has been approved by the U.S. Food and Drug Administration.

The Patient Information leaflet was last revised: January 2011.

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