PRODUCT MONOGRAPH

PrXOLEGEL™

ketoconazole topical gel, 2% w/w

Antifungal Agent

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Table of Contents

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ketoconazole topical gel, 2% w/w

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Topical	topical gel / 2% w/w	See DOSAGE FORMS, COMPOSITION and PACKAGING for a complete list of nonmedicinal ingredients.

INDICATIONS AND CLINICAL USE

XOLEGEL™ (ketoconazole topical gel 2% w/w) is indicated for the topical treatment of moderate to severe seborrheic dermatitis in immunocompetent adults and children 12 years of age or older.

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

Geriatrics (> 65 years of age):
Evidence from clinical studies suggests that use in the geriatric population is not associated with differences in safety or effectiveness. See WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics for more information.

Pediatrics (< 12 years of age):
XOLEGEL™ is not indicated for use in patients under 12 years of age. See WARNINGS AND PRECAUTIONS.

CONTRAINDICATIONS

XOLEGEL™ is contraindicated in those patients with a history of sensitivity reactions to ketoconazole, or any other component of this product, including the container (see DOSAGE FORMS, COMPOSITION AND PACKAGING). For a complete list of non-medicinal ingredients, see SUMMARY PRODUCT INFORMATION, above.

Cross-sensitivity with other azole antifungals is possible.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Gels are flammable. Note: Keep away from heat and flame. Keep tube tightly closed.

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

For topical use on the skin only.

Not for ophthalmic, oral or intravaginal use. Avoid contact with mucous membranes and open wounds. In the event of accidental contact, the affected area should be rinsed thoroughly with warm water.

General

If a reaction suggesting hypersensitivity or chemical irritation should occur, or if the disease worsens, use of the medication should be discontinued. The patient should be reassessed after an appropriate period of time if the XOLEGEL™ has been discontinued for any of these reasons.

If a patient is on chronic therapy with a topically applied corticosteroid, tapering of the dose should be considered rather than an abrupt discontinuation to avoid a rebound phenomenon. XOLEGEL™ is not a corticosteroid; it has a different mechanism of action and is not associated with the corticosteroid rebound phenomenon.

In the clinical trials of XOLEGEL™, no other topical medication or moisturizer, except routinely used cleansers and cosmetics, were applied concomitantly with XOLEGEL to the areas being treated. Subjects were asked to wait at least 20 minutes after application of XOLEGEL™ before applying cosmetics or sunscreen.

Carcinogenesis and Mutagenesis

Long term topical carcinogenicity studies have not yet been completed and there are no data available on long term topical carcinogenicity. See TOXICOLOGY: Carcinogenicity

Endocrine and Metabolism

Although not observed in clinical trials with topical ketoconazole, oral ketoconazole treatment may inhibit the synthesis of cortisol and testosterone.

Hepatic/Biliary/Pancreatic

Although not observed in clinical trials with topical ketoconazole, hepatotoxicity has been reported with oral ketoconazole treatment.

Immunocompromised Patients

The safety and efficacy of XOLEGEL™ in immunocompromised patients have not been studied.

Ophthalmologic

Ketoconazole has been found to be an eye irritant and contact with the eyes should be avoided.

Sensitivity/Resistance
Cross-sensitivity with miconazole and other imidazoles may exist and caution is suggested when XOLEGEL™ is used in patients with known sensitivities to imidazoles.

Sexual Function/Reproduction
Ketoconazole has been shown to be embryotoxic and teratogenic (syndactylia and oligodactylia) in the rat when given in the diet at 80 mg/kg/day. Evidence of maternal toxicity and embryotoxicity was seen with doses as low as 10 mg/kg. Ketoconazole has been found to impair reproductive performance in female (decreased pregnancy and implantation rates) and male (increased abnormal sperm and decreased sperm motility) rats.

Skin
Skin irritation was observed in pre-clinical and clinical studies. Use of XOLEGEL™ should be discontinued if irritation develops.

Special Populations
Pregnant Women: There are no adequate studies using XOLEGEL™ in pregnant women. Systemic absorption of XOLEGEL™ is minimal when used as recommended. However there have been reports of limb defects in newborns exposed to ketoconazole in the first trimester. Ketoconazole is teratogenic in rats when administered orally at a dose of 80 mg/kg (10 times the maximum recommended oral human dose). XOLEGEL™ should only be used in pregnant women when the benefits outweigh the risks.

Nursing Women: Ketoconazole is excreted in breast milk. Caution should be exercised when XOLEGEL™ is administered to a nursing woman.

Pediatrics (< 12 years of age): Safety and effectiveness in pediatric patients below the age of 12 have not been studied. See ADVERSE REACTIONS section of this Product Monograph for information on adolescent pediatric patients.

Geriatrics (> 65 years of age): Of the 933 subjects in the three vehicle-controlled clinical efficacy and safety 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

Adverse Drug Reaction Overview

Most treatment-emergent adverse events in clinical trials were associated with the administration site and skin, most commonly application site burning. Treatment emergent adverse events were generally transient in nature and resolved upon discontinuation of the treatment. In subjects receiving multiple courses of treatment, the incidence of treatment emergent adverse events generally declined over time.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

The safety of XOLEGEL™ was assessed in nine clinical trials that included: four Phase 1 studies consisting of one single-dose study and three repeat-dose studies, one Phase 2 pharmacokinetic study, three Phase 3 vehicle-controlled studies, and a long-term safety study. This resulted in 1395 subjects being exposed to XOLEGEL™. In the three Phase 3 studies, a total of 388 subjects were exposed to the gel vehicle. Safety results from the three vehicle-controlled studies were integrated due to their similar design parameters and inclusion criteria, and are presented in Table 1.

Table 1: Overall Summary of Adverse Events Reported by ≥ 1% of Subjects All Phase 3 Vehicle-Controlled Studies

System Organ Class Preferred Term	Gel Vehicle N=388 n (%)	XOLEGEL™ GEL N=545 n (%)
Any Adverse Event	67 (17.3)	89 (16.3)
Eye Disorders	2 (0.5)	6 (1.1)
Gastrointestinal Disorders	6 (1.5)	2 (0.4)
General Disorders And Administration Site Conditions	17 (4.4)	33 (6.1)
Application site burning	12 (3.1)	23 (4.2)
Application site reaction	4 (1.0)	1 (0.2)
Infections and Infestations	13 (3.4)	14 (2.6)
Nasopharyngitis	4 (1.0)	4 (0.7)
Injury, Poisoning and Procedural Complications	2 (0.5)	8 (1.5)
Nervous System Disorders	8 (2.1)	8 (1.5)
Headache	3 (0.8)	6 (1.1)
Respiratory, Thoracic and Mediastinal Disorders	5 (1.3)	10 (1.8)
Skin and Subcutaneous Tissue Disorders	8 (2.1)	10 (1.8)

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.

Less Common Clinical Trial Adverse Drug Reactions (< 1%)

Those events occurring at a rate < 1% and which were deemed related to treatment (possible, probable, certain) in all subjects treated with either XOLEGEL™ (n = 1072) or gel vehicle control (n = 388) in Phase 3 clinical studies and the long term safety study are listed below. Those events occuring only in the long term safety study are marked with an asterisk.

Eye Disorders: erythema of eyelid*; eye irritation; eyelid oedema*; eyelids pruritus*; eye swelling; lacrimation increased*; keratoconjunctivitis sicca
Gastrointestinal Disorders: nausea*.
General Disorders and Administrative Site Conditions: application site dermatitis; application site discharge; application site dryness; application site erythema; application site

irritation; application site pain; application site pruritus; application site reaction; pain*; pyrexia*.
Infections and Infestations: application site pustules; ear infection*; ear lobe infection*; folliculitis*; impetigo*; impetigo nos; influenza*; nasopharyngitis*; otitis externa*; sinusitis*; upper respiratory tract infection*.
Neoplasms benign, malignant and unspecified (incl. cysts and polyps): pyogenic granuloma.
Nervous System Disorders: dizziness; paraesthesia.
Respiratory, Thoracic and Mediastinal Disorders: cough*; dyspnoea*; nasal congestion*; pharyngolaryngeal pain*; rhinorrhoea*; sinus congestion*
Skin and Subcutaneous Tissue Disorders: acne; dermatitis*; dermatitis acneiform*; dermatitis contact*; dermatitis nos; dry skin; eczema*; erythema; nail discoloration; pain of skin; pruritus; pruritus aggravated; rash*; rash scaly*; rosacea* swelling face.

Abnormal Hematologic and Clinical Chemistry Findings
Hematologic and clinical chemistry parameters were not monitored during clinical trials with XOLEGEL™.

Long Term Safety
In an open-label, non-controlled, long-term (up to 52 weeks) safety study 527 subjects received multiple courses of treatment as needed. The safety results were supportive of those from the three vehicle-controlled studies. Adverse events related to application site burning and application site reaction generally decreased as the study progressed with no reports of these events during the last three months of the study. The percentage of subjects reporting treatment-related AEs during the first quarter was 7.6%. This percentage decreased during the course of the study to 0.7% for the last quarter of the year-long trial.

Pediatric Safety
Twenty-six pediatric patients were evaluated for safety, 12 in the pivotal study and 14 in the long-term safety study. Subjects ranged in age between 12 and 17 years. A total of 18 subjects received XOLEGEL ™ treatment and 8 subjects received gel vehicle treatment. Six of the 26 pediatric subjects experienced 12 adverse events. Only one of these subjects, randomized to the gel, experienced a treatment-related adverse event -- stinging and burning at application site. The remaining adverse events reported by pediatric patients were unrelated to treatment and most were also reported by > 1% of the overall study population.

Dermal Safety
Contact sensitization, cumulative irritation, phototoxicity and photoallergy studies were conducted in human volunteers with XOLEGEL™. Under the conditions of study, XOLEGEL™ did not demonstrate contact sensitization, phototoxicity or photoallergenicity, but did demonstrate potential to cause irritation. XOLEGEL™ did not demonstrate photocarcinogenicity potential in a mouse assay.

Post-Market Adverse Drug Reactions
No information is available at this time.

DRUG INTERACTIONS

Overview

Formal drug interaction studies with XOLEGEL™ have not been performed. In clinical trials in which no other topical medication or moisturizers applied to the affected areas during the study were permitted, no drug interactions were reported with XOLEGEL™. Based on very low plasma concentrations observed after topical application, drug interactions are not expected. Oral ketoconazole has been observed to have drug-drug and drug-food interactions.

DOSAGE AND ADMINISTRATION

Recommended Dose

It is recommended that a thin layer should be applied to the affected and immediately surrounding areas once daily for 14 days.

Missed Dose

If a dose is missed, the patient may apply it as soon as convenient, or wait until the next scheduled time of application.

Administration

XOLEGEL™ GEL is intended for topical use only.

The patient should be advised to:

1. Wash their hands before and after application of XOLEGEL™ to the affected area;
2. Clean the affected area, then apply a thin layer of XOLEGEL™ to the affected and immediately surrounding areas;
3. Wait at least 20 minutes before applying cosmetics or sunscreen;
4. Avoid washing treated areas for 3 hours following application;
5. Apply XOLEGEL™ to newly affected areas that appear during the course of treatment;
6. Avoid applying other products to the treated areas for the duration of treatment, including medicated shampoos to treat seborrheic dermatitis of the scalp;
7. Follow the full course of therapy to reduce the possibility of recurrence.

If there is no response within the recommended treatment period, the diagnosis should be re-evaluated.

OVERDOSAGE

There has been no experience of overdose with XOLEGEL™. No incidents of accidental ingestion have been reported. If oral ingestion occurs, symptomatic treatment is recommended.

ACTION AND CLINICAL PHARMACOLOGY

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 know as Pityrosporum ovale), which leads to the death of the organism.

Mechanism 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.

Pharmacokinetics

Absorption: Eighteen subjects (10 males and 8 females), ranging in age from 19 to 70 years (average 45.4 years), with severe seborrheic dermatitis 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. Measured plasma concentrations ranged from below the limit of quantification (<0.1 ng/mL) to 13.9 ng/mL.

Table 2 Summary of XOLEGEL ™'s Pharmacokinetic Parameters in Patients with Severe Seborrheic Dermatitis

	C_{max} (ng/mL) N = 18		Cmin (ng/mL) N = 18		Tmax (h) N = 16		AUCτ (ng.h/mL) N = 18	
	Days 7 - 8	**Days 14 - 15**	**Days 7 - 8**	**Days 14 - 15**	**Days 7 - 8**	**Days 14 - 15**	**Days 7 - 8**	**Days 14 - 15**
Median	0.52	0.52	0.22	0.21	7.88	7.00	10.08	8.88
Range	<LLOQ–13.94	<LLOQ–5.36	<LLOQ–2.97	<LLOQ–2.06	2.00–24.68	3.78-24.00	<2.40-196.83	<2.40-117.08

Distribution, metabolism and excretion of XOLEGEL™ were not studied due to the low systemic exposure following topical administration.

Special Populations and Conditions:
Pediatrics (< 12 years of age): Safety and effectiveness in pediatric patients below the age of 12 have not been established.

Geriatrics (> 65 years of age): Of the 933 subjects in the three vehicle-controlled clinical efficacy and safety 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.

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

SPECIAL HANDLING INSTRUCTIONS

Keep out of reach of children.

Serious Warnings and Precautions

Gels are flammable. Note: Keep away from heat and flame. Keep tube tightly closed.

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

XOLEGEL™ is supplied in 2 g and 15 g epoxy-lined, blind-end, aluminum tubes.

Each gram of XOLEGEL™ 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.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

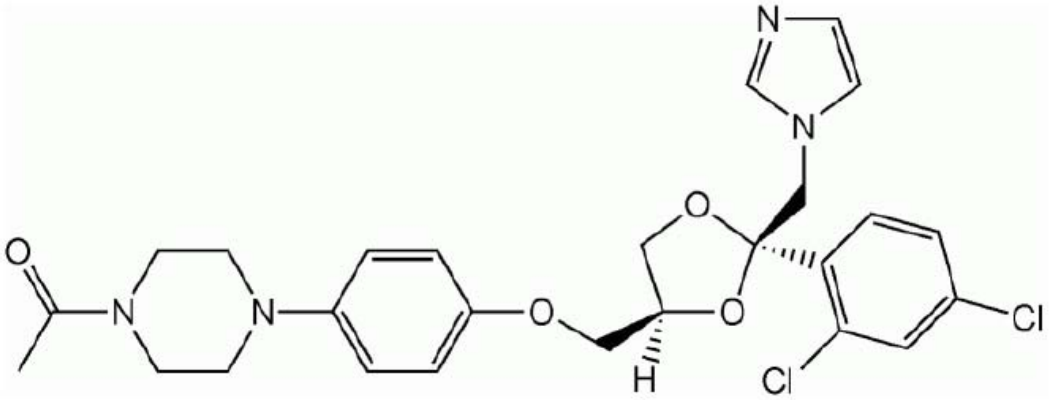
Proper name: ketoconazole

Chemical name: (±)-*cis*-1-Acetyl-4-[p-[[2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-piperazine

Molecular formula: $C_{26}H_{28}Cl_2N_4O_4$

Molecular mass: 531.43

Structural formula:



Physicochemical properties:

Appearance: White to off-white powder

Melting Point: 148° -152°C

Solubility: Practically insoluble in water; soluble in dichloromethane, methanol, ethanol, propylene glycol and polyethylene glycol.

CLINICAL TRIALS

Study demographics and trial design

Table 3: Summary of patient demographics for pivotal clinical study

	Pivotal Study		Subset of subjects aged 12 – 17 years	
	XOLEGEL™ GEL	VEHICLE CONTROL	XOLEGEL™ GEL	VEHICLE CONTROL
Age (years)*				
N	229	230	4	8
Mean	51.96	50.43	15.25	14.9
Gender (%)				
Male	59.4	59.1	25.0	37.5
Female	40.6	40.9	75.0	62.5

The pivotal study 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™, 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.

No microbiological assessment was included in this study, or other clinical trials.

Study results

The proportion of patients effectively treated in the pivotal study is shown in the following table.

Table 4: Pivotal Study

	XOLEGEL™ GEL N=229	Vehicle Control N=230
Proportion of patients effectively treated	58 (25.3%, 95% CI 19.8 - 31.5)	32 (13.9%, 95% CI 9.7 - 19.1)

CI = confidence interval

Two additional double-blind, randomized, vehicle-controlled, parallel, and multi-center studies that included a total of 316 patients treated with XOLEGEL™ provided supportive evidence of the efficacy of XOLEGEL™ for treatment of seborrheic dermatitis. Patients 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 patients who were effectively treated, as defined in the pivotal study, at Day 28.

TOXICOLOGY

Single Dose Toxicity

Species	Route of Administration	Lethal Dose LD_{50} (mg of ketoconazole/kg)	
		Male	**Female**
Mice	Oral	786	618
Mice	Oral	300	
Mice	Intravenous	46.6	41.5
Rats	Oral	287	166
Rats	Oral	200	
Rats	Intravenous	85.9	85.9
Guinea pigs	Oral	178	226
Guinea pigs	Intravenous	23.3	32.5
Dogs	Oral	937	640
Dogs	Intravenous	42.4	56.3

When mice were treated with a single oral gavage dose of 2% ketoconazole shampoo, decreased activity and diarrhea occurred. Clinical signs in rats were similar to those observed in mice and included decreased activity, diarrhea, slight vocalization when touched, as well as fluid around the nose and mouth.

Repeat Dose Toxicity: Tabular Summary

Species / Strain	Delivery route	Duration	Dose (mg/kg/day)	No of animals per group	Results
Mice/CD-1	Topical	90 days	0, 40, 80, 160, 400 mg/kg Ketoconazole gel (varying concentrations)	10/sex/gp (plus 54 more for toxicokinetics)	No treatment related changes in mortality, clinical observations, body weight, food consumption, or ophthalmology. The 400 mg/kg dose group was discontinued early due to the severity of the dermal irritation observed. Dermal irritation also occurred at 160 mg/kg but to a much lesser degree. Significant increases in AST and ALT in females at 160 mg/kg with no associated microscopic hepatic changes associated with liver function. Brown discoloration of the liver in all males and females treated with 400 mg/kg, 9 males treated with 160 mg/kg, and 5 females treated with 80 mg/kg. Thyroid weight increased in treated males; not associated with any microscopic changes. Treated animals exhibited dose related increases in epidermal hyperplasia of the skin, pigment accumulation in the liver, and hypertrophy (minimal/mild) of epithelial cells in collecting ducts of the kidney medulla. NOAEL was 40 mg/kg.
Rat/Sprague-Dawley	topical (abraded/non-abraded skin)	28 days*	0, 40 mg/kg Ketoconazole 2% gel	10/sex/gp	Ketoconazole gel treated animals appeared similar to control animals in terms of clinical observations, dermal irritation, body weights, food consumption. No treatment related dermal irritation was observed. NOAEL was 40 mg/kg.
Rabbit/NZW	topical (abraded/non-abraded skin)	28 days	0, 40 mg/kg Ketoconazole 2% gel	10/sex/gp	Ketoconazole gel treatment had no adverse effects on clinical signs, body weights, food consumption, clinical pathology, or ophthalmoscopy. NOAEL was 40 mg/kg.
Rabbit/NZW	Topical (abraded/non-abraded skin)	21 days (5 days/week)	0, 40 mg/kg Ketoconazole 2% cream	5/sex/gp	Administration of 2% ketoconazole cream at a dose of 40 mg/kg for 21 days did not cause dermal irritation or result in treatment related adverse effects. The NOAEL was determined to be 40 mg/kg.
Minipig/Hanford	topical	29 or 30 days	0, 240 mg/kg Ketoconazole 2% gel	3/sex/gp	No treatment related adverse effects on survival, bodyweights, organ weights, food consumption, heart or respiration rate, ophthalmology, dermal irritation, gross pathology, or histopathology. No treatment-related effects on dermal irritation. NOAEL was 240 mg/kg.

* study terminated on days 17 and 18 due to excessive toxicity of desonide (another arm in the study tested a combination of ketoconazole and desonide).

Genotoxicity: Tabular Summary

Type of Study	Species	Route	Duration and Dose		Results
Reverse mutation in bacterial cells	S. typhimurium	In vitro	NAV		Ketoconazole was found to be non-mutagenic to *Salmonella typhimurium* in the presence and absence of metabolic activation
Reverse mutation in bacterial cells	S. typhimurium E. coli with and without metabolic activation	In vitro	52 ± 4 hours Dose range: 0.133/0.003 to 100/2.5 ketoconazole/desonide combination µg/plate, respectively		The ketoconazole-desonide combination product did not significantly increase the number of revertant colonies in the presence or absence of S9 metabolic activation.
Chromosome aberrations	Chinese Hamster Ovary Cells with and without metabolize activation	In vitro	3, 17.8 hours incubation Positive Control: MMC, CP Ketoconazole/ Desonide combination:		The ketoconazole-desonide combination did not induce chromosomal aberrations in CHO cells.
			Assay 1: 7.08 / 0.177 10.1 / 0.253 14.4 / 0.361 20.6 / 0.515 29.4 / 0.735 42.0 / 1.05 60.0 / 1.50 µg/mL	Assay 2: 1.25 / 0.031 2.50 / 0.063 5.00 / 0.125 10.0 / 0.250 15.0 / 0.375 20.0 / 0.500 30.0 / 0.750 40.0 / 1.00 50.0 / 1.25 µg/mL	
Dominant Lethal Mutation	Mice	Oral	Single dose 20, 80, 320 mg/kg Positive Control: CP Formulation/vehicle NAV		Ketoconazole doses of up to 320 mg/kg did not cause dominant lethal mutations in male mouse germ cells.
Dominant Lethal Mutation	Mice	Oral	Single dose 20, 80, 320/160 mg/kg Formulation/vehicle NAV		Ketoconazole doses of 20 and 80 mg/kg did not induce dominant lethal mutations in female germ cells. At the 320/160 mg/kg dose level, an increase in the number of late fetal deaths occurred. These fetal deaths appeared to be caused by direct toxicity of the high doses of ketoconazole and not from mutations.
Bone marrow micronuclei	Mice	Intraperitoneal	2 doses – 24 hours apart 0, 20, 40, 80 mg/kg		Ketoconazole was not clastogenic in this test system.

Type of Study	Species	Route	Duration and Dose	Results
			Positive Control: CP Formulation/vehicle NAV	
Bone marrow micronuclei	Mice	Oral	Single dose Ketoconazole/Desonide combination in corn oil vehicle: 0 350/8.75 375/9.375 700/17.5 750/18.75 1400/35.0 1500/37.5 mg/kg Positive Control: CP	Under the conditions of this study, both the ketoconazole/desonide combination was considered to be negative for clastogenicity.
Bone marrow micronuclei	Mice	Oral	Single dose Ketoconazole/Desonide combination in gel vehicle 0 0.10 / 0.0025 0.20 / 0.05 0.40 / 0.01mg/kg Positive Control: CP	One animal at the high dose exhibited an increase in the number of micronucleated PCEs; however, no other animals at this or any dose level exhibited a response. This animal was considered to be an outlier and was not included in the analysis. In the remainder of animals, the combination of ketoconazole and desonide in a gel vehicle did not cause any significant increases in micronucleated PCEs and under conditions of this assay, was not clastogenic.

NAV = data not available
CP: cyclophosamide; MMC: mitomycin C

Carcinogenicity

Long term topical carcinogenicity studies have not yet been completed and no data are available on long term topical carcinogenicity.

Albino Swiss mice and Wistar rats both received doses of 0, 5, 20 and 80 mg/kg per day of ketoconazole administered via the diet for 18 months and 24 months respectively. There were no statistically significant differences between groups in the incidence or type of tumours.

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.

Reproductive and Developmental Toxicity

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.

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. See following pages for a tabular summary of data.

Local Tolerance and Other Studies

The local effects of ketoconazole were investigated in dermal irritation studies in rabbits and dogs and in ocular irritation studies in rabbits. In dermal irritation studies, 0.15% and 1% ketoconazole shampoo was found to cause mild to moderate irritation and 2% shampoo caused severe irritation; however, 2% ketoconazole cream did not cause dermal irritation. In ocular irritation studies, 0.15 % and 0.3% ketoconazole shampoo did not cause ocular irritation, but 1% and 2% solutions caused ocular irritation. Ketoconazole treatment did not have a toxic effect on the conjunctiva or cornea of rabbits. Intravitreal injections of up to 0.54 mg did not cause ocular toxicity. See following pages for a tabular summary of data.

Carcinogenicity: Tabular Summary

Type of Study	Species	Route	Duration and Dose	Results
Photocarcinogenicity	Mice	Topical	40 weeks treatment plus 12 weeks observation 0, 5 mg/kg with UV radiation Ketoconazole gel, and placebo gel	Topical administration of ketoconazole gel did not produce any evidence of photocarcinogenicity under conditions of this study. The incidence and time to appearance of tumours in animals treated with ketoconazole was similar to that of untreated and placebo treated animals.
Feeding Study	Mice	Oral	18 months 5, 20, 80 mg/kg	Ketoconazole added to the feed for 18 months did not induce carcinogenesis.
Feeding Study	Rats	Oral	2 years 5, 20, 80 mg/kg	Ketoconazole added to the feed for 24 months was not carcinogenic to rats.

NAV = not available

Reproductive and Developmental Toxicity: Tabular Summary

Type of Study	Species	Route	Duration and Dose	Results
Fertility and Early Embryonic Development to Implantation				
Segment I	Rats	Oral	F0 ♂: 60 days before mating; F0 ♀: 14 days before mated & during gestation 0, 10, 20, 40, & 80 mg/kg	Ketoconazole doses of ≤ 40 mg/kg had no teratogenic effects, no effects on fertility, gestation, or pup viability. Ketoconazole in doses of 80 mg/kg caused maternal toxicity (decrease body weight), mortality, a decrease in pregnancy rates, embryotoxicity and teratogenicity (absence of metacarpal and metatarsal bones and abnormal heads)..
Early Pregnancy & Decidual Cell Response	Rats	Oral	DG 1 – 8 Exp 1: 0, 10, 30, 100, 300 mg/kg Exp 2: 0, 25, 50, 75 mg/kg Exp 3: 0, 25, 50, 75, 100 mg/kg Exp 4: 75 mg/kg	The results of these studies suggest that high doses of ketoconazole (≥ 75 mg/kg) can significantly reduce ovarian progesterone secretion. Since, progesterone is necessary for successful implantation and pregnancy, the interference of ketoconazole with ovarian steroidogenesis may provide a plausible explanation for the spontaneous abortions generally seen in animals treated with high doses of ketoconazole
Male Fertility	Rats	Oral	8 or 13 weeks 0, 25, 75 mg/kg	Treatment with 75 mg/kg/day resulted in reduced sperm motility, reduced plasma testosterone levels, and increased amounts of abnormal sperm (mostly detached sperm heads). A 30 to 34% decrease in pregnancy rate was seen in females paired with males treated with 75 mg/kg/day. At 25 and 75 mg/kg/day histopathological changes were noted in the adrenals and testes. These changes included increased focal tubular atrophy and hyperplasia of Leydig cells (testes), vacuolation of zona fasiculata (adrenals), as well as hyperplasia and hypertrophy of the zona glomerulosa (adrenals). No adverse effects were noted in the untreated females or fetuses (after external examination only).
Male Fertility	Rats	Oral	Single Dose :0, 3, 6, 12, 24 mg/kg 0 or 24 mg/kg/day for 30, 60 or 90 days.	A single 40 mg/kg dose was associated with a decrease in dihydrotestosterone and testosterone. After 30, 60, and 90 days of treatment, the proportion of abnormal sperm increased, sperm number decreased, and percent of motile sperm decreased. There was also a decrease in fertility rates. No changes were seen in the weight of

Type of Study	Species	Route	Duration and Dose	Results
				the testis, seminal vesicle, epididymis, or prostate. In addition, no changes were seen in testicular germ cell counts.
Male Fertility	Rats	Intraperitoneal	14 days 1, 4, 10 mg	Animals treated with 10 mg of ketoconazole had undetectable serum testosterone levels for the entire sampling period (1 hour - 336 hours post 1st dose). In addition, animals treated intraperitoneally with 10 mg were lethargic, had diarrhea, and were emaciated. Deaths were seen in 50% of the animals in the 10 mg dose group and no cause could be determined.
Effect on Embryo-Fetal Development				
Embryotoxicity	Mouse	Oral	DG 6 – 18 0, 10, 20, 40 mg/kg	Oral administration of 0, 10, 20, or 40 mg/kg ketoconazole to pregnant female mice on GD 6-18 did not produce maternal toxicity. In the 20 and 40 mg/kg dose groups, increased resorptions, stillbirths, and lengths of gestation were noted. Decreased birth weights were seen in pups from the 40 mg/kg group. When compared to controls, late descent of testes and vaginal opening was observed in many of the pups from treated dams.
Embryotoxicity	Rats	Oral	DG 6 – 15 0, 10, 40, 160 mg/100 mg food	No treatment related abnormalities were seen at dose up to 40 mg/100 mg food. The 160 mg dose resulted in an increase in the number of dead fetuses and decreases in pregnancy rates, maternal food consumption, litter sizes, pup weight at delivery, and the number of live fetuses. This dosage was also teratogenic (oligodactyly and syndactyly).
Embryotoxicity	Rats	Oral	DG 6 – 15 0, 10, 20, 40, 80, 160 mg/100 mg food	Teratogenic effects including oligodactyly and syndactyly were seen at 80 mg per 100 grams of food and embryotoxicity was seen at 160 mg per 100 grams of food.
Embryotoxicity	Rats	Oral	DG 6 – 15 0, 10, 40, 160 mg/kg	A 95% mortality rate was seen in the high dose group. Also, when compared to controls, there were twice as many litters with resorptions in the dams treated with 40 mg/kg.
Embryotoxicity	Rats	Oral	DG 6 – 15 0, 2.5, 10, 40 mg/kg	At the 40 mg/kg dose, there was a decrease in litter sizes and an increase in the number of dead fetuses (32%

Type of Study	Species	Route	Duration and Dose	Results
				stillborn); however, there were no missing metacarpal or metatarsal bones
Embryotoxicity	Rats	Oral	DG 6 – 21 0, 10, 25, 50 mg/kg	0, 10, 25, or 50 mg/kg did not produce overt signs of maternal toxicity or cause maternal death. However, all dams treated with 50 mg/kg had a delay in the onset of parturition (3 days). Fully formed live and dead fetuses, as well as an increased number of resorption sites were found. Pups from the 25 mg/kg group exhibited decreased birth weights. Late descent of testes and delayed vaginal opening were observed in pups from treated dams.
Embryotoxicity	Rabbits	Oral	DG 6 – 18 0, 10, 40 mg/kg	Doses of 10 and 40 mg/kg did not produce the same teratogenic effects that were seen in rats. Only 35% of inseminated rabbits became pregnant and the mortality rate was 10% in the 40 mg/kg group. There were no differences in litter sizes, fetus weight at delivery, or number of live fetuses amongst the treatment groups. When compared to controls, resorptions were greater in both the 10 and 40 mg/kg groups. Although there did not seem to be the same teratogenic effects in rabbits as in rats, the drug does appear to affect rabbits in the early stages of pregnancy.
Peri & Post-natal Development				
	Rats	Oral	DG 16 – DL 21 0, 10, 40, 160 mg/100g food	In the 160 mg/100 g food group, a 10% mortality rate was noted and a substantial decrease was seen in pregnancy rates, maternal weight gain, and food consumption. The mid and high dose groups exhibited an increase in gestation period, number of dead fetuses, and cannibalism as well as decreased litter sizes. Individual fetal body weights and pup body weight gains were significantly decreased in the 160 mg/kg group.
	Rats	Oral	DG 16 – DL 21 0, 10, 40, 80 mg/kg	In the 80 mg/kg group, only 2 out of 20 treated dams survived the study. In the 40 mg/kg dose group, the following were noted: decreased maternal weight gain, decreased maternal food consumption, increased length of gestation, increased cannibalism, and increased

Type of Study	Species	Route	Duration and Dose	Results
				number of stillborn fetuses (49%). All pups from the 40 mg/kg group died a few days after birth and no live pups were born to the remaining dams in the 80 mg/kg group. The NOAEL for maternal toxicity and fetal toxicity was 10 mg/kg
Effects on pre and postnatal development including maternal function.	Rats	Oral	DG 14 – DL 3 0, 12.5, 25, 50 mg/kg	There was a dose-related increase in length in gestation. When compared to control values, litter sizes were decreased by ketoconazole treatment of 25 and 50 mg/kg/day. At 5 months of age, male offspring were sacrificed and examined. In the male offspring of treated dams, there were no reproductive tract malformations or retention of nipples. Male offspring from the 50 mg/kg/day group had slightly but not significant decreases in epididymal weights, seminal vesicle weights, and testes weights.

DG = day of gestation. DL = day of lactation. NAV = data not available

Local Tolerance: Tabular Summary

Type of Study	Species	Route	Duration and Dose	Results
Dermal Irritation	Rabbits	Topical	30 days 0, 500, 1000, 2000 mg/kg cream formulation	Treatment with ketoconazole cream did not result in an increase in dermal irritation. In both the placebo and ketoconazole treated groups, a small amount of dermal irritation (primary irritation index of 0.17-0.36) was noted.
Dermal Irritation	Rabbits	Topical	Duration: NAV 0.15%, 1.0% shampoo	The results indicated that the 0.15% ketoconazole shampoo was a mild irritant and the 1% shampoo was a moderate irritant. Primary Dermal Irritation Index Scores of 1.9 and 4.8 were given to the 0.15% and 1% ketoconazole solutions, respectively
Dermal Irritation	Rabbits	Topical	7 days 0.3 mL of 2% shampoo	Using the Draize Primary Dermal Irritation Index, the 2% ketoconazole shampoo formulation was classified as a severe irritant and given a score of 6.7
Dermal Irritation	Dogs	Topical Intact and abraded skin	28 days 80 mg of 2% cream formulation	Treatment with ketoconazole 2% cream did not result in dermal irritation.
Dermal Irritation	Dogs	Intravaginal pessary	5 days 400 mg	Treatment with ketoconazole administered as a pessary did not result in vaginal irritation.
Ocular Irritation	Rabbits	Ocular	Duration: NAV Exp 1: 0.3% or 2% shampoo Exp 2: 0.15 % or 1% shampoo	The results of these studies indicated that 0.15% and 0.3% ketoconazole shampoo solutions were negative for ocular irritancy; however, the vehicle control, the 1% solution, and the 2% solution were all found to be positive ocular irritants.
Ocular Irritation	Rabbits	Ocular	Up to 14 days 0, 1 % solution	Ketoconazole 1% solution did not significantly retard the closure of epithelial defects. In addition, the mean scores for conjunctival injection, stromal edema, haze, iritis, and the quality of regenerating epithelium for ketoconazole treated eyes were not significantly different from the control values.
Ocular Irritation	Rabbits	Ocular	3 weeks 0, 1%, 3%, 5% solution	Treatment with ketoconazole solutions of varying concentrations did not have a toxic effect on the conjunctiva or the cornea of the rabbits. Hyperaemia was seen in both control and test animals but was not considered significant lesions caused by drug irritation. Specifically, a “small amount” of hyperaemia was observed in a total of 6/18 eyes treated with the vehicle

				alone, 2/6 eyes treated with 1% ketoconazole, and in 3/6 eyes treated with 3% ketoconazole. Mild and moderate hyperaemia was seen in 2/6 eyes treated with 5% ketoconazole
Ocular Irritation	Rabbit	Ocular	Single Dose 2% Topical Gel*	The results indicated that both placebo gel and 2% ketoconazole gel were mild irritants. All irritation was reversed by 72 hours after treatment.

NAV = Data not available
* Similar to XOLEGEL™

REFERENCES

Elewski MD, Ling MR, Phillips, TJ, Efficacy and Safety of a New Once-Daily Topical Ketoconazole 2% Gel in the Treatment of Seborrheic Dermatitis: A Phase III Trial, J. Drugs Derm., 2006, 5 (7), 646 – 650.

PART III: CONSUMER INFORMATION

[Pr]XOLEGEL™
ketoconazole topical gel, 2% w/w

This leaflet is part III of a three-part "Product Monograph" published when XOLEGEL™ was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about XOLEGEL™. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
XOLEGEL™ is a prescription medication for the treatment of seborrheic dermatitis, a common inflammatory scaling disease affecting certain areas of the skin.

What it does:
XOLEGEL™ is a topical antifungal agent which helps to kill the fungus believed to be one of the causes of seborrheic dermatitis. It does this by interfering with the growth of the cell membrane of the fungus.

When it should not be used:
XOLEGEL™ should not be used if you are allergic to ketoconazole or any of the other ingredients of XOLEGEL™ GEL (See What the nonmedicinal ingredients are).

XOLEGEL™ is not for ophthalmic, oral, or intravaginal use.

What the medicinal ingredient is:
Ketoconazole

What the nonmedicinal ingredients are:
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, D&C Yellow No. 10.

What dosage forms it comes in:
XOLEGEL™ comes in a smooth, clear amber gel formulation containing 2% ketoconazole, which will spread evenly and smoothly on affected areas. It contains no artificial fragrance.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Gels are flammable. Note: Keep away from heat and flame. Keep tube tightly closed.

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

BEFORE you use XOLEGEL™ talk to your doctor or pharmacist if:

- **You are pregnant or likely to become pregnant**
- **You are breast feeding or planning to breastfeed**
- **You are allergic to ketoconazole or any of the other ingredients in XOLEGEL™**
- **You are taking any other medications, including topical corticosteroids.**

Avoid contact with the mouth, nose, eyes or open wounds. To avoid any accidental contact, you should wash your hands thoroughly after each application. In the event of accidental contact, the affected area should be rinsed thoroughly with warm water.

INTERACTIONS WITH THIS MEDICATION

While no drug interactions have been reported in clinical studies with XOLEGEL™, no drug-drug interaction studies have been conducted.

PROPER USE OF THIS MEDICATION

Usual Adult Dose: the usual adult dose is a thin layer of gel applied to the affected and immediately surrounding area once a day for 14 days. It is important that you use XOLEGEL™ every day for the full 14 days or as recommended by your doctor, to reduce the possibility of recurrence. You should consult your doctor if your condition worsens or does not improve by the end of treatment.

How to apply XOLEGEL™: Wash your hands before and after applying the medication. Clean the affected area and spread a thin layer of XOLEGEL™ evenly on the affected area(s) with your fingertips. Be sure to cover all affected areas and the immediately surrounding skin. Do not cleanse the areas where medication is applied for at least three hours after application. Wait at least 20 minutes after application before applying routine cosmetics or sunscreens.

XOLEGEL™ should be applied to newly affected areas that appear during the course of treatment. You should avoid applying other products to the treated areas while you are using XOLEGEL™, including medicated shampoos to treat seborrheic dermatitis of the scalp.

If you are taking topical corticosteroids, your doctor may give you directions to gradually lessen your dose over time until you stop taking the corticosteroid, or he/she provides you with other directions.

Missed Dose: If you miss a dose, continue with your usual dosing schedule. Do not double dose.

Overdose: In case of accidental oral ingestion, contact your doctor or local emergency care facility.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

XOLEGEL™ may be irritating to the mouth, nose, eyes and open wounds (See Warnings and Precautions).

No serious adverse events related to XOLEGEL™ were reported in clinical trials. The most common side effect is burning or reaction on the skin where XOLEGEL™ has been applied.

This is not a complete list of side effects. For any unexpected effects while taking* XOLEGEL™*, contact your doctor or pharmacist.

HOW TO STORE IT

Store XOLEGEL™ at room temperature (15 – 30ºC).

Keep out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs . If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
toll-free fax 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, Barrier Therapeutics Canada Inc., at:

1-800-440- 5507

or

PO Box #2730
Richmond Hill, Ontario
L4E 1A7

This leaflet was prepared by
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