P R O D U C T M O N O G R A P H

PrGynazole•1®

(Butoconazole Nitrate)

Vaginal Cream 2%, USP

Therapeutic Classification

Antifungal

Ferring Inc.
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July 23, 2004

Control Number: 091390

NAME OF DRUG

PrGYNAZOLE•1®

(Butoconazole Nitrate) Vaginal Cream 2% USP

Ferring Standard

THERAPEUTIC CLASSIFICATION

Antifungal

ACTIONS / CLINICAL PHARMACOLOGY

GYNAZOLE•1 (butoconazole nitrate) vaginal cream 2%, contains butoconazole nitrate 2%, an imidazole derivative with antifungal activity.

Like other imidazole derivatives, butoconazole nitrate presumably exerts its antifungal activity by altering cellular membranes, resulting in increased membrane permeability, secondary metabolic effects, and growth inhibition. Although the exact mechanism of action of butoconazole nitrate has not been fully determined, it has been suggested that the fungistatic activity of the drug may result from interference with ergosterol synthesis, probably via inhibition of C-14 demethylation of sterol intermediates (e.g. lanosterol). Like some other imidazole derivatives (e.g. miconazole), the fungicidal activity of butoconazole at high concentrations may result from a direct physicochemical effect of the drug on the fungal cell. This effect may involve hydrophobic interactions between the drug and unsaturated fatty acid components of the membrane.

Butoconazole has some antibacterial activity against gram-positive organisms, but this effect cannot be explained on the basis of inhibition of ergosterol synthesis since bacteria generally do not contain membrane sterols. It has been suggested that the antibacterial effect of butoconazole and other imidazole derivatives may be similar to

the physicochemical effect of these agents on fungi or may involve other metabolic sites.

INDICATIONS AND CLINICAL USE

Gynazole•1 (butoconazole nitrate) vaginal cream 2%, is indicated for the local treatment of vulvovaginal infections caused by *Candida albicans*. The diagnosis should be confirmed by KOH smears and/or cultures.

Note: GYNAZOLE•1 is safe and effective in non-pregnant women; however, the safety and effectiveness of this product in pregnant women has not been established (SEE PRECAUTIONS).

CONTRAINDICATIONS

GYNAZOLE•1 is contraindicated in patients with a history of hypersensitivity to any of the components of the product.

WARNINGS

This cream contains mineral oil. Mineral oil may weaken latex or rubber products such as condoms or vaginal contraceptive diaphragms; therefore, use of such products within 72 hours following treatment with GYNAZOLE•1 is not recommended.

Recurrent vaginal yeast infections, especially those that are difficult to eradicate, can be an early sign of infection with the human immunodeficiency virus (HIV) in women who are considered at risk for HIV infection.

PRECAUTIONS

General : If clinical symptoms persist, tests should be repeated to rule out other pathogens, to confirm the original diagnosis, and to rule out other conditions that may predispose a patient to recurrent vaginal fungal infections.

Appropriate microbiologic studies should be performed to confirm the diagnosis and rule out infection caused by nonsusceptible pathogens when an adequate response is not achieved following a course of butoconazole therapy. Patients should be instructed not to rely on condoms or diaphragms to prevent sexually transmitted diseases or pregnancy during butoconazole nitrate therapy, since the cream may damage these devices and result in protective failure. Alternative methods of birth control should be used. Patients also should be instructed not to use tampons while using intravaginal butoconazole nitrate vaginal cream.

Butoconazole nitrate vaginal cream should not be applied to the eye nor administered orally. Patients receiving butoconazole nitrate vaginal cream should be instructed to contact their physician or local poison control centre immediately if they accidentally ingest the vaginal cream.

Patients also should be advised to consult a clinician if manifestations of vulvovaginitis recur within 2 months of therapy, or if they think that they may have been exposed to HIV. Recurrent infection may be a sign of pregnancy or a serious underlying condition such as AIDS or diabetes mellitus.

Butoconazole nitrate vaginal cream should not be used in women with diabetes mellitus or who are HIV-positive or have AIDS unless otherwise directed by a clinician. Patients who are considering use of butoconazole nitrate vaginal cream should be advised not to use the drug if abdominal pain, fever, or a foul-smelling vaginal discharge is present.

Nursing : It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when butoconazole nitrate is administered to a nursing woman.

Pediatrics: Safety and effectiveness in children have not been established.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Carcinogenesis: Long term studies in animals have not been performed to evaluate the carcinogenic potential of this drug.

Mutagenicity: Butoconazole nitrate was not mutagenic when tested in the Ames bacterial test, yeast gene conversion, chromosomal aberration assay in CHO cells, CHO/HGPRT point mutation assay, mouse micronucleus, and rat dominant lethal assays.

Impairment of Fertility: No impairment of fertility was seen in rabbits or rats administered butoconazole nitrate in oral doses up to 30 mg/kg/day (3 times the human dose based on mg/M^2) or 100 mg/kg/day (10 times the human dose based on mg/M^2), respectively.

Pregnancy:

In pregnant rats administered 6 mg/kg/day of butoconazole nitrate intravaginally during the period of organogenesis, there was an increase in resorption rate and decrease in litter size; however, no teratogenicity was noted. This dose represents a 130 - to 353-fold margin of safety based on serum levels achieved in rats following intravaginal administration compared to the serum levels achieved in humans following intravaginal administration of the recommended therapeutic dose of butoconazole nitrate. Butoconazole nitrate has no apparent adverse effect when administered orally to pregnant rats throughout organogenesis at dose levels up to 50 mg/kg/day (5 times the human dose based on mg/M^2). Daily oral doses of 100, 300 or 750 mg/kg/day (10, 30 or 75 times the human dose based on mg/M^2 respectively) resulted in fetal

malformations (abdominal wall defects, cleft palate), and maternal stress was also evident at these higher dose levels. There were, however, no adverse effects on litters of rabbits who received butoconazole nitrate orally, even at maternally stressful dose levels (e.g., 150 mg/kg, 24 times the human dose based on mg/M^2).

Butoconazole nitrate, like other azole anti-fungal agents, causes dystocia in rats when treatment is extended through parturition. However, this effect was not apparent in rabbits treated with as much as 100 mg/kg/day orally (16 times the human dose based on mg/M^2). There are, however, no adequate and well-controlled studies in pregnant women. GYNAZOLE•1 should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

ADVERSE REACTIONS

Of the 314 patients treated with GYNAZOLE•1 for 1 day in controlled clinical trials, 18 patients (5.7%) reported complaints such as vulvar/vaginal burning, itching, soreness and swelling, pelvic or abdominal pain or cramping, or a combination of two or more of these symptoms. In 3 patients (1%) these complaints were considered treatment-related. Five of the 18 patients reporting adverse events discontinued the study because of them.

Although hepatocellular dysfunction has occurred during systemic treatment with imidazole-derived antifungal agents (e.g. ketoconazole), this adverse event has not been reported to date following intravaginal butoconazole nitrate therapy.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There is no specific treatment for butoconazole overdose; therefore, management of the patient should consist of symptomatic and supportive therapy.

DOSAGE AND ADMINISTRATION

The recommended dose of GYNAZOLE•1 is one applicator of cream (approximately 5 grams of the cream) intravaginally as a single dose treatment. This amount of cream contains approximately 100 mg of butoconazole nitrate.

Butoconazole nitrate vaginal cream is for intravaginal administration only and should not be administered orally; contact with the eyes should be avoided.

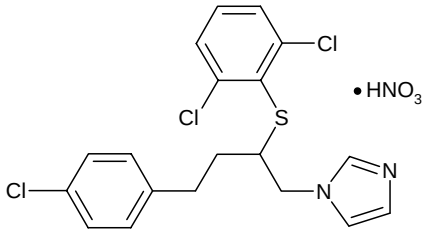
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper name: (Butoconazole nitrate)

Chemical name: (±)-1-[4-(P-chlorophenyl)-2-[(2,6-dichlorophenyl) [thiobutyl] imidazole mononitrate

Chemical Structure:



Butoconazole Nitrate

Molecular formula: $C_{19}\ H_{18}\ Cl_3\ N_3\ O_3\ S$

Molecular weight: 474.79

Description: Butoconazole nitrate is a white to off-white crystalline powder. It is sparingly soluble in methanol; slightly soluble in chloroform, methylene chloride, acetone, and ethanol; very slightly soluble in ethyl acetate; and practically insoluble in water. It melts at about 159°C with decomposition.
The drug has a pk_a of approximately 6.7.

DRUG PRODUCT

Trade Name: GYNAZOLE•1

Composition: GYNAZOLE•1 contains 2% butoconazole nitrate in a cream of edetate disodium, glyceryl monoisostearate, methylparaben, mineral oil, polyglyceryl-3 oleate, propylene glycol, propylparaben, colloidal silicon dioxide, sorbitol solution, purified water and microcrystalline wax.

Storage: Store at room temperature 15°to 30°C (59°to 86°F). Avoid heat above 30°C (86°F).

AVAILABILITY OF DOSAGE FORM

Availability: GYNAZOLE•1 (butoconazole nitrate) vaginal cream 2%, is available in cartons containing one single-dose prefilled disposable applicator (approximately 5 grams of the cream).

GYNAZOLE.1 (Butoconzole Nitrate)

INFORMATION FOR THE CONSUMER

Read this information carefully. It has been prepared by Ferring Inc. to help you get the most benefit from this medicine. It contains general points about this medicine and should add to more specific advice from your doctor or pharmacist.

This information should not replace your doctor's or pharmacist's advice. Because of your health condition, they may have given you different instructions. If so, be sure to follow their advice. Also, if you have any questions or concerns after reading this information, talk to your doctor or pharmacist.

WHAT IS GYNAZOLE•1 VAGINAL CREAM?

GYNAZOLE•1 is an antifungal medication. It helps prevent fungus from growing. GYNAZOLE•1 vaginal cream is used to treat vaginal candida (yeast) infections.

WHAT DOES GYNAZOLE LOOK LIKE?

One pre-filled applicator of GYNAZOLE•1 contains 5 grams of cream with approximately 100 mg of butoconazole nitrate.

WHAT IS A VAGINAL YEAST INFECTION?

The type of fungus that is primarily responsible for vaginal yeast infections is called Candida albicans. Candida is a type of yeast that is normally present in the body. Usually, it's a small and harmless inhabitant of the mouth, intestine, and vagina. When, for some reason, the normal environment of the vagina is altered, the Candida can begin to grow rapidly and further upset the normal vaginal conditions. When this happens, you get a yeast infection.

WHAT ARE THE SYMPTOMS OF VAGINAL YEAST INFECTION?

The primary symptom of a vaginal yeast infection is itching, usually on the external genital area. You may also experience burning, especially during urination or intercourse, and have a vaginal discharge that is thick and white with a texture similar to cottage cheese.

WHAT IS IN GYNAZOLE•1 VAGINAL CREAM?

This medicine contains an active drug called butoconazole nitrate. It also contains non-medicinal ingredients: edetate disodium, glyceryl monoisostearate, methylparaben, mineral oil, polyglyceryl-3 oleate, propylene glycol, propylparaben, colloidal silicon dioxide, sorbitol solution, purified water and microcrystalline wax.

WHAT SHOULD I KNOW <u>BEFORE</u> I USE GYNAZOLE VAGINAL CREAM?

Do not use condoms or a vaginal contraceptive diaphragm for 3 days after you use this medicine. The mineral oil in this medicine can weaken latex or rubber products. This might make condoms and a diaphragm less effective and you will not be fully protected.

DO NOT USE GYNAZOLE.1 IF

- You have diabetes mellitus unless otherwise directed by a physician
- You are HIV positive or have AIDS unless otherwise directed by a physician
- If abdominal pain, fever or a foul smelling discharge is present
- You are allergic to butoconazole nitrate or any of its ingredients

Do not use this medicine if you are pregnant or breast feeding unless your doctor has told you to.

CALL YOUR DOCTOR IF:

- You notice worsening of, or new vaginal symptoms (vaginal discharge, itchiness, odour).
- If the infection persists after treatment.
- You experience any other unusual or unexpected effects.
- If symptoms re-occur within 2 months of therapy or if you think you may have been exposed to HIV.

HOW SHOULD I TAKE GYNAZOLE•1 VAGINAL CREAM?

Instructions for Patients

Using the GYNAZOLE•1 Prefilled Disposable Applicator

3 Easy Steps:

Step 1: Preparing the Applicator

Peel back the protective foil and remove the prefilled applicator. Applicator is designed to be used with tip in place.

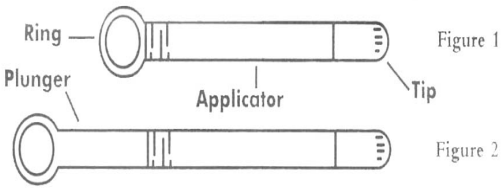


Figure 1

Figure 2

Do *not* remove tip; do *not* use applicator if tip has been removed.

Do not warm applicator before using. While holding the applicator firmly, pull the ring back to *fully* extend the plunger (*See Figure 2*).

Step 2: Inserting the Applicator

Gently insert the applicator into the vagina as far as it will comfortably go (*See Figure 3*).

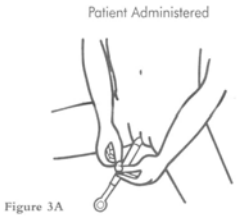


Figure 3A

Figure 3B

Step 3: Applying the Cream

Push the plunger to release the cream (*See Figure 4**).*** Remove the empty applicator from the vagina and throw it away.


Figure 4A

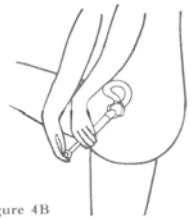


Figure 4B

Figure 4C

Important Instructions:

- One prefilled applicator of GYNAZOLE•1 should be administered as a single dose.
- This cream contains mineral oil. Mineral oil may weaken latex or rubber products such as condoms or vaginal contraceptives and diaphragms; therefore, use of such products within 72 hours following treatment with GYNAZOLE•1 is not recommended.
- There are no adequate and well-controlled studies in pregnant women.

GYNAZOLE•1 should be used during pregnancy only under the supervision of a physician.

Do not apply GYNAZOLE•1 to the eye or take orally. Please contact your physician or local poison control centre immediately if GYNAZOLE.1 is accidentally ingested.

REMEMBER THIS MEDICINE IS FOR YOU ONLY. ONLY A DOCTOR CAN PRESCRIBE IT FOR YOU. NEVER GIVE IT TO SOMEONE ELSE EVEN IF THEIR SYMPTOMS ARE THE SAME AS YOURS.

KEEP IN A SAFE PLACE OUT OF THE REACH OF CHILDREN.

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Microbiology

The spectrum of activity for butoconazole nitrate was determined through in vitro assays for antibacterial, antifungal and antitrichomonal activity.

The in vitro antibacterial activity was determined as described in Table 1. This table presents the minimum inhibitory concentrations of butoconazole nitrate against the bacterial isolates tested. The gram-positive bacteria tested were inhibited by butoconazole nitrate with S. pyogenes being the most sensitive. The only species of gram-negative bacteria inhibited by butoconazole nitrate was K. pneumoniae**.**

Butoconazole nitrate was found to have in vitro activity against Candida albicans as well as the major genera of dermatophytic fungi. As shown in Table 2, butoconazole nitrate, miconazole nitrate and clotrimazole had comparable in vitro activity against C. albicans. All three compounds inhibited 100% of the strains tested at concentrations of 10 mcg/ml or less.

Table 1 (AT 1873)
The In Vitro Antibacterial and Antitrichomonas Activity of Butoconazole Nitrate

	MIC[1] (ug/ml)
Staphylococcus aureus	6.25
Streptococcus faecalis	3.12
Streptococcus pyogenes	0.0016
Escherichia coli	>200.00
Klebsiella pneumoniae	6.25
Serratia marcescens	>200.00
Pseudomonas aeruginosa	>200.00
Proteus mirabilis	>200.00
	MLC[1] (ug/ml)
Trichomonas foetus	100.00

[1] Minimum Inhibitory Concentrations (MIC) and Minimum Lethal Concentrations (MLC) were determined using a microdilution broth procedure.

Table 2 (AT 1873)
The In Vitro Antifungal Activity of Butoconazole Nitrate

		Concentration (ug/ml) and Cumulative Percent Inhibited						
Compound/Organics	No. Tested	<0.05	0.05	0.1	0.5	1.0	5.0	10
Butoconazole Nitrate								
Candida albicans	31				3.2	6.5	61	100
Trichophyton mentagrophytes	2					50	100	
Trichophyton rubrum	2		50		100			
Trichophyton tonsurans	2						100	
Trichophyton concentricum	1		100					
Microsporium canis	2			50		100		
Microsporium gypseum	2		50			100		
Epidermophyton floccosum	1						100	

[1]Minimal Inhibitory Concentrations (MIC) were determined using agar dilution procedure.

PHARMACOLOGY

Following vaginal administration of butoconazole nitrate vaginal cream 2%, to 3 women, 1.7% (range 1.3 - 2.2%) of the dose was absorbed on average. Peak plasma levels (13.6 - 18.6 ng radioequivalents/ml of plasma) of the drug and its metabolites are attained between 12 and 24 hours after vaginal administration.

Absorption : Small amounts of butoconazole nitrate are slowly absorbed systemically when the drug is administered intravaginally. Following intravaginal administration of approximately 5 g of radiolabeled butoconazole nitrate 2% cream (approximately 100 mg of the drug total) in healthy women, peak plasma concentrations 24 hours after administration have ranged from 19-44 ng/ml. Radioactivity was apparent in plasma 2-8 hours after intravaginal administration and persisted for 4-5 days. Based on limited pharmacokinetic data, it is estimated that about 5.5% of an intravaginal dose of butoconazole nitrate reaches systemic circulation.

Distribution : Distribution of butoconazole nitrate into body tissues and fluids following intravaginal administration has not been determined. Butoconazole nitrate crosses the blood-brain barrier and the placenta in animals following IV and intravaginal administration, respectively, but it is not known whether this occurs in humans. It is not known whether the drug is distributed into milk.

Elimination : The metabolic fate of butoconazole nitrate following intravaginal administration has not been fully characterized, but systemically absorbed drug appears to be extensively metabolized, probably in the liver. Following intravaginal

administration of approximately 5 g of radiolabeled butoconazole nitrate 2% cream (approximately 100 mg of the drug total) in healthy adults, the plasma half-life of the drug reportedly ranges from 21-24 hours. The systemically absorbed fraction of an intravaginal dose of butoconazole nitrate appears to be excreted in approximately equal proportions in urine and faeces. Approximately 2.7 and 2.8% of an intravaginal dose of the drug reportedly is excreted in urine and faeces, respectively, within 4-7 days, principally as unidentified metabolites; unchanged drug is not detectable.

Pharmacokinetics

Three studies were conducted to examine the pharmacokinetics and local tolerance in female subjects. In one study, three female patients with vulvovaginal candidiasis were given a single dose of butoconazole nitrate cream containing 84-89 mg of butoconazole nitrate radiolabeled with tritium. Blood, urine and faecal samples were collected at specified time intervals for seven days. In a period of 7 days, an average of 1.11 ± 0.38 (mean ± S.D.) and 0.59 ± 0.37 of the dose was recovered from urine and faeces, respectively. Overall, an average of 1.7% of the dose was recovered in the excreta. Based on the excretion data, the extent of vaginal absorption of butoconazole nitrate 2% in women with vulvovaginal candidiasis was determined to be 1.7% of the administered dose.

The second study performed was done to study the amount and rate of absorption, and the routes of excretion of butoconazole nitrate after its vaginal administration.

Three female volunteers were each given a single dose of vaginal cream containing 90-110 mg of butoconazole nitrate radiolabeled with tritium. Blood, urine and faecal samples were collected at specified time intervals for seven days.

The plasma half-life ($t_{½}$) of butoconazole nitrate radioequivalents (total radioactivity) was estimated by linear regression analysis of log plasma concentrations. The half-lives of total radioactivity in two of the subjects were estimated to be 21 and 24 hours (Table 3).

Table 3

Pharmacokinetic Parameters Of Butoconazole Nitrate Radioequivalents In Human Subjects Given A Single Intravaginal Dose Of Approximately Five Grams Of A Formulated Cream Containing 2% [^{3}H]-Butoconazole Nitrate

		Plasma Values[a]	
Subject	t max (hr)	C max (ng equivalents/ml)	t ½ (hr)
1	24	27.4	ND
	24	19.3	21
2	24	35.9	24
Mean ±SE	24±0	27.5±4.8	22.5

[a]Plasma concentrations were normalized to a dose of 1.71 mg/kg; values shown are those obtained after correcting for volatile radioactivity in each plasma sample.

t max = time of maximum plasma concentration.

C max = highest plasma concentration.

Half-lives (t ½) were computed from plasma concentrations obtained at 24, 48 and 72 hours (Subject A.A.), and at 24, 48, 72 and 96 hours (Subject M.N.).

ND - not determined (no 48-hour value).

Recovery of Dose from Vagina

After a 12-hour drug exposure, the dose was washed from the vagina of each subject and the vaginal wash was assayed for total radioactivity. Seventy-nine to 92 percent (87±4%, mean ± SE) of the administered dose was recovered in the vaginal wash. The overall recovery of radioactivity in excreta and vaginal wash thus accounted for 86 to 97% (93 ± 4%) of the vaginal dose. The rate of absorption of butoconazole nitrate radioequivalents from the vaginal mucosa is slow with measurable levels of radioactivity observed between two and eight hours after vaginal dose administration.

The third study determined the absorption and excretion of butoconazole nitrate in patients with vulvovaginal candidiasis.

Three female volunteers were each given a single dose of vaginal cream containing 75-78 mg of butoconazole nitrate radiolabeled with tritium. Blood, urine and faecal samples were collected at specified time intervals for seven days.

Absorption of the dose in all three subjects was slow. Detectable levels of radioactivity were not observed until two hours after the vaginal dose was administered. Maximum plasma concentrations were reached between 12 and 24 hours. Pharmacokinetic results are outlined in Table 4. Pharmacokinetic parameters are listed in Table 4.

Table 4

Pharmacokinetic Parameters Of [^{3}H]-Butoconazole Nitrate In Plasma Following Intravaginal Application In Women With Vulvovaginal Candidiasis

Parameter	Subject 1	Subject 2	Subject 3	Mean ± S.D.
Dose[1]	75.3	78.2	75.8	76.4 ± 1.55
Body weight[2]	58.6	90.9	81.4	77.0 ± 16.6
Dose/kg[3]	1.29	0.86	0.93	1.03 ± 0.23
Cmax[4]	31.8	16.5	22.5	23.6 ± 7.71
Tmax[5]	12	24	24	20.0 ± 6.93
T 1/2[5]	47.9	50.8	30.9	43.2 ± 10.7
AUC[6]	1796.8	1016.2	1116.7	1309.9 ± 424.7
AUC/Dose/kg[7]	1392.8	1181.6	1200.8	1258.4 ± 116.8

[1]Dose in mg of butoconazole nitrate.
[2]Body weight in kilograms.
[3]Milligrams of butoconazole nitrate/kg body weight.
[4]Cmax = ng-eq/ml corrected for the amount of volatile radioactivity.
[5]In hours.
[6]AUC for 0-144 hours. Units are ng-eq/ml•hr.
[7]Units are $\frac{\text{(ng-eq)•hr•kg}}{\text{ml•mg}}$

TOXICOLOGY

Topical and Local Tolerance Toxicity

Dermal irritation studies were conducted by applying butoconazole formulations to intact and abraded skin on the backs of rabbits. The 2.31% suppository formulation was not irritating. The 1.93% intravaginal cream formulation did cause signs of irritation. The study was repeated using the 1.93% cream and its vehicle cream. Both the butoconazole and vehicle cream caused signs of irritation.

Guinea pig dermal sensitization studies were conducted with the 2.31% butoconazole soft elastic gelatin suppository formulation and a 1.93% butoconazole intravaginal cream. Neither formulation produced signs of sensitization.

Three studies were conducted with various butoconazole formulations to evaluate their potential to cause vaginal irritation. Each formulation was administered daily for 10 days. Three sections from each vagina were examined microscopically and scored according to the amount of mucosal ulceration, leukocytic infiltration, oedema, and congestion. A sham-treated group and a positive-control group (miconazole nitrate) were included in each study. Minimal to moderate (clinically acceptable) irritation was noted for the wax-based insert vehicle, 2.23% and 4.42% wax-based insert formulations; two vehicle creams and their respective 2% butoconazole creams; the currently marketed cream, an “improved cream” (with EDTA and dimethicone) with and without 2% butoconazole, and a formulation with glycerin instead of propylene glycol with and without 2% butoconazole. The only unacceptable formulation, due to production of marked irritation, was a 2.31% butoconazole soft elastic gelatin suppository, the development of which was abandoned.

Table 5

DERMAL IRRITATION STUDIES				
SPECIES (N)	**DURATION**	**DOSE**	**FORMULATION**	**OBSERVATIONS**
Rabbit (females) (6)	Single dose with 4-day observation period.	0.5 ml per site	2.31% vaginal soft elastic gelatin suppository	No signs of irritation were observed.
Rabbit (males) (6)	Single dose with 7-day observation period.	0.5 ml per site	1.93% cream	Slight to severe erythema and slight oedema was observed 2 to 7 days after dosing.
Rabbit (males) (6)	Single dose with 7-day observation period.	0.5 ml per site	1.93% cream	Erythema was observed 4 hours to 7 days after dosing.

Table 6

VAGINAL IRRITATION/TOLERANCE STUDIES		
SPECIES	**FORMULATION**	**OBSERVATIONS**
Rabbit	Sham control	
	Wax-based Insert - vehicle	Mild irritation.
	Wax-based Insert - 2.23% butoconazole	Moderate irritation.
	4.42% butoconazole	Moderate irritation.
	Soft elastic gelatin suppository 2.31% butoconazole	Marked irritation.
	Wax-based suppository - 3.90% miconazole	Mild irritation.
Rabbit	Sham control	Mild irritation.
	SR* vehicle A	Moderate irritation.
	SR vehicle A + 2% butoconazole	Moderate irritation.
	SR vehicle C	Mild irritation.
	SR vehicle C + 2% butoconazole	Mild irritation.
	2% miconazole	Moderate irritation.
Rabbit	Sham control	Minimal irritation.
	Improved cream vehicle	Mild irritation.
	Improved cream + 2% butoconazole	Minimal irritation.
	Marketed cream + 2% butoconazole	Mild irritation.
	Cream vehicle with glycerin	Mild irritation.
	Cream vehicle with glycerin + 2% butoconazole	Mild irritation.
	2% miconazole	Mild irritation.

SR* = sustained release

Table 7

ACUTE TOXICOLOGY			
SPECIES	**ROUTE**	**LD_{50}**	**OBSERVATIONS**
Mouse	Oral	The acute oral LD_{50} is greater than 3200 mg/kg.	Signs of toxicity seen in 2 males and 1 female given 3200 mg/kg included decreased activity, intermittent seizures, rough coat, pallor, unthrifty appearance, and wasting.
Mouse	IP	The acute IP LD_{50} is greater than 1600 mg/kg.	A dose-related decrease in activity was noted. The female that died exhibited decreased activity, pallor, rough coat, unthrifty appearance and wasting.
Rat	Oral	The acute oral LD_{50} was calculated to be 1720 mg/kg for female rats and greater than 3200 mg/kg for male rats.	Signs of toxicity included decreased activity, rough coat, ataxia, pallor, laboured respiration, red crust around the nose, unthrifty appearance, and anogenital stain.
Rat	IP	The acute IP LD_{50} was calculated to be 940 mg/kg.	Signs of toxicity included decreased activity, rough coat, ataxia, pallor, chromodacryorrhea, and unthrifty appearance and were seen in the groups given 800 mg/kg or 1600 mg/kg. One male given 400 mg/kg exhibited unthrifty appearance, rough coat, and pallor 1 to 7 days postdosing.
Dog	Oral	It was not possible to calculate an LD_{50} value.	No signs of toxicity were seen in the female. The male exhibited dacryorrhea, diarrhea, and vomiting on the day of dosing.

TABLE 8

Multidose Toxicity Studies

Key: NDE = No drug-related effect
NDU = no drug used

SPECIES	ROUTE	CLINICAL SIGNS	PATHOLOGY
Rat	Vaginal	NDU	NDU
	Sham		
	0.1 ml/day vehicle	NDU	NDU
	0.1 ml/day	NDE	NDE
	1.93% butoconazole		
Rat	Vaginal Sham	NDU	NDU
	0.2 ml/day vehicle	NDU	Evidence of mild vaginal irritation.
	0.2 ml/day	Transient staining, redness,	Evidence of mild
	1.93% butoconazole	and/or swelling of the external genitalia	vaginal irritation.
	0.2 ml/day	Transient staining, redness	Evidence of mild
	2.0% miconazole	and/or swelling of the external genitalia	vaginal irritation.

Key: NDE = No drug-related effect
NDU = no drug used

SPECIES	ROUTE	CLINICAL SIGNS	PATHOLOGY
Rat	Vaginal	NDU	Microscopic evidence of vaginal irritation in 2 rats.
	Sham		
	0.1 ml/day vehicle for suppository	NDU	Microscopic evidence of vaginal irritation in 3 rats.
	0.1 ml/day 2.31% butoconazole suppository formulation	Some rats had staining of external genitalia during the first 2 months. A slight decrease in body weight gain was noted.	Microscopic evidence of vaginal irritation in 15 rats.
Rat	Oral (gavage)		
	0 (untreated)	NDU	NDU
	0 (vehicle)	NDU	NDU
	10	NDE	NDE
	33	NDE	Males had nephropathy
			Males had nephropathy
	100	NDE	
Rat	Oral (gavage)		
	0	NDU	NDU
	10	NDE	NDE
	33	NDE	NDE
	100	NDE	NDE
Rabbit	Vaginal, 1 empty suppository/day	NDU	NDU
	1 suppository with vehicle/day	NDU	NDU
	1 suppository with 2.31% butoconazole/day	NDE	NDE

Key: NDE = No drug-related effect
NDU = no drug used

SPECIES	ROUTE	CLINICAL SIGNS	PATHOLOGY
Dog	Vaginal, 1 empty suppository/day	NDU	NDU
	1 suppository with vehicle/day	NDU	NDU
	1 suppository with 2.31% butoconazole/day	NDE	NDE
Dog	Vaginal	NDU	NDU
	Sham		
	0.2 ml/kg/day vehicle	NDU	NDU
	0.2 ml/kg/day 1.93% butoconazole	A slight red crusty deposit around the external genitalia was seen in 2 dogs.	NDE
	0.3 ml/kg/day 2.0% miconazole	NDE	NDE
Dog	Oral (capsules)	NDU	—
Dog	Oral (capsules)	NDU	NDU
Monkey	Vaginal	NDU	NDU
	Sham		
	0.2 ml/day vehicle	NDU	NDU
	0.2 ml/day 1.93% butoconazole	NDE	NDE
	0.2 ml/day 2.0% miconazole	NDE	NDE

Teratogenicity Studies

Reproductive effects from oral administration of butoconazole nitrate to pregnant rats included an increase in the gestation period, difficult labour, or decreased neonatal survival. When administered during organogenesis intravaginally to rats or orally at 50 mg/kg to rats and at 150 mk/kg to rabbits, no teratogenicity was seen. At high maternally toxic oral doses (i.e. 100 mk/kg and higher) administered during organogenesis to the rat, abdominal wall defects and cleft palate were seen. The no-effect oral dose in the rat teratology studies is at least 100 fold greater than the human systemic dose.

Mutagenicity Studies

The mutagenic potential of butoconazole nitrate was evaluated in vitro using 5 strains of Salmonella typhimurium and one strain of Saccharomyces cerevisiae. The test was carried out with and without mammalian microsomal activation. Butoconazole nitrate was not mutagenic in any of these test systems. No evidence of mutagenicity was noted in a mouse micronucleus test in which mice were orally administered butoconazole nitrate.

Carcinogenisis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies were not considered necessary for butoconazole nitrate because the duration of therapy is short and systemic absorption is low. Additionally, no proliferative lesions were observed in the oral or vaginal toxicity studies conducted for up to 3 or 6 months, respectively. There were no positive results in the short-term mutagenicity tests, both in vitro (Ames, yeast gene conversion) and in vivo (male

dominant lethal, mouse micronucleus). Structurally, butoconazole nitrate is not closely related to known carcinogens; therefore, no carcinogenicity studies were conducted with butoconazole nitrate based on its intended use, chronic toxicity study results, lack of mutagenic potential and structure.

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