

PRODUCT MONOGRAPH

**PrTERAZOL \* 3**  
terconazole  
Vaginal Ovules

**PrTERAZOL \* 7**  
terconazole  
Vaginal Cream

**PrTERAZOL \* 3**  
terconazole  
Vaginal Cream

**PrTERAZOL \* 3 DUAL-PAK\***  
terconazole  
Vaginal Ovules and Cream

Antifungal Agent

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Janssen Ortho Inc.  
19 Green Belt Dr.  
Toronto, Ontario  
M3C 1L9

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**CLINICAL PHARMACOLOGY**

The exact pharmacologic mode of action of terconazole is uncertain; however, it may exert its antifungal activity by disruption of normal fungal cell membrane permeability. Terconazole exhibits fungicidal activity *in vitro* against the genus *Candida*. Both the yeast and mycelial forms of *C. albicans* are sensitive to terconazole.

Following intravaginal administration of terconazole in humans, absorption ranged from 5%-8% in three hysterectomized patients and 12%-16% in two non-hysterectomized subjects with tubal ligations. After single and multiple doses of terconazole 0.4% (20 mg) vaginal cream, the mean peak plasma concentration for both treatments was 0.004 µg, indicating no accumulation of terconazole following repeated intravaginal dosing.

### **INDICATIONS AND CLINICAL USE**

TERAZOL 3 terconazole 80 mg Vaginal Ovules, TERAZOL 7 terconazole 0.4% Vaginal Cream and TERAZOL 3 terconazole 0.8% Vaginal Cream are indicated for the local treatment of vulvovaginal candidiasis (moniliasis). The diagnosis of monilial infection should be confirmed by microscopic examination of a KOH smear and/or by culture.

TERAZOL ovules and cream may be used in pregnant patients during the second and third trimesters if the physician considers it essential to the welfare of the patient (see PRECAUTIONS, Use in Pregnancy). The therapeutic effect of TERAZOL products is not affected by oral contraceptive usage, menstruation or previous monilial infection.

### **CONTRAINDICATIONS**

Patients known to be hypersensitive to terconazole or to any components of the ovule or cream.

### **WARNINGS**

None.

### **PRECAUTIONS**

#### **General**

TERAZOL terconazole cream and ovules should be discontinued and patients should not be re-treated if sensitization, vulvovaginal irritation, fever, chills or flu-like symptoms are reported during use.

Photosensitivity reactions were observed in some normal volunteers following repeated dermal application of terconazole 2.0% and 0.8% creams under conditions of filtered artificial ultraviolet light. Photosensitivity reactions have not been observed in clinical trials in patients who were treated vaginally with terconazole 0.4%, 0.8% or 1.6% vaginal cream.

The base contained in the ovule formulation may interact with certain natural rubber products, such as those used in vaginal contraceptive diaphragms or condoms. Concurrent use is not recommended. Therapy with TERAZOL 7 or TERAZOL 3 cream may be considered for use under these conditions.

If there is a lack of response to TERAZOL therapy, appropriate microbiological studies (standard KOH smear and/or cultures) should be repeated to confirm the diagnosis and rule out other pathogens.

Intractable candidiasis may be the presenting symptom of unrecognized diabetes mellitus. In these cases, appropriate diagnostic tests for diabetes should be done.

#### Use in Children

Safety and efficacy in children have not been established.

#### Use in Pregnancy

Terconazole should not be used in the first trimester of pregnancy.

In studies, over 600 pregnant patients have used terconazole during the second and third trimesters with no apparent adverse effect on the course of pregnancy. These studies have not shown increased risk of abnormalities when administered during this period.

Pregnant patients should be advised to exercise caution in the use of the vaginal applicator.

Nursing Mothers

It is not known whether terconazole is excreted in human milk. Should the decision be made to use this drug, nursing should be discontinued during therapy.

**ADVERSE REACTIONS**

During controlled clinical studies conducted in the United States, 284 patients with vulvovaginal candidiasis were treated with terconazole 80 mg vaginal ovules, 521 patients were treated with terconazole 0.4% vaginal cream and 297 patients were treated with terconazole 0.8% vaginal cream.

TERAZOL 3 terconazole 80 mg Vaginal Ovules

Based on comparative analyses with placebo and a standard agent, the adverse experiences considered adverse reactions most likely related to terconazole 80 mg vaginal ovules were:

<u>Event</u>	<u>TERAZOL</u>	<u>Placebo</u>
Headache	30.3%	20.7%
Pain (female genitalia)	4.2%	0.7%
Burning	15.2%*	11.2%
Body Pain	3.9%*	1.7%
Fever	2.8%	1.4%
Chills	1.8%	0.75%

\*Not statistically significantly different from placebo

The adverse drug experience on terconazole 80 mg ovules most frequently causing discontinuation was burning (2.5% vs. 1.4% with placebo) and pruritus (1.8% vs. 1.4% with placebo). The terconazole therapy-related dropout rate was 3.5% and the placebo therapy-related dropout rate was 2.7%.

TERAZOL 7 terconazole 0.4% Vaginal Cream

Based on comparative analyses with placebo and a standard agent, the adverse experiences considered to be most likely related to terconazole 0.4% vaginal cream were:

<u>Event</u>	<u>TERAZOL</u>	<u>Placebo</u>
Headache	26.0%	17.0%
Body Pain	2.1%	0.0%
Fever	1.75%	0.5%
Chills	0.4%	0.0%

Vulvovaginal burning (5.2%), itching (2.3%) or irritation (3.1%) occurred less frequently with terconazole 0.4% vaginal cream than with the vehicle placebo. The adverse drug experience most frequently causing discontinuation of treatment with terconazole cream was vulvovaginal itching (0.6%), which was lower than the incidence for placebo (0.9%). The terconazole therapy and the placebo therapy-related dropout rate was 1.9%.

TERAZOL 3 terconazole 0.8% Vaginal Cream

Based on comparative analyses with placebo and a standard agent, the only adverse experiences considered adverse reactions to terconazole 0.8% vaginal cream were:

<u>Event</u>	<u>TERAZOL</u>	<u>Placebo</u>
Headache	21.0%	16.0%
Dysmenorrhea	6.0%	2.0%

Fever (1.0% vs. 0.3% with placebo) has been reported. The therapy-related dropout rate was 2.0%. The adverse drug experience on terconazole 0.8% most frequently causing discontinuation was vulvovaginal itching (0.7%), which was similar to the incidence for placebo (0.3%).

## **SYMPTOMS AND TREATMENT OF OVERDOSAGE**

Overdose of terconazole in humans has not been reported to date.

## **DOSAGE AND ADMINISTRATION**

### **TERAZOL 3 terconazole 80 mg Vaginal Ovule**

One TERAZOL 3 Vaginal Ovule (80 mg of terconazole) is administered intravaginally once daily at bedtime for three consecutive days.

### **TERAZOL 7 terconazole 0.4% Vaginal Cream**

One applicatorful (5 g) of TERAZOL 7 Vaginal Cream (20 mg of terconazole) is administered intravaginally once daily at bedtime for seven consecutive days. In addition, a thin layer of TERAZOL 7 Vaginal Cream (0.4% terconazole) is applied for seven consecutive days directly to the vulva and massaged in gently.

### **TERAZOL 3 terconazole 0.8% Vaginal Cream**

One applicatorful (5 g) of TERAZOL 3 Vaginal Cream (40 mg terconazole) is administered intravaginally once daily at bedtime for three consecutive days. In addition, a thin layer of TERAZOL 3 Vaginal Cream (0.8% terconazole) is applied for three consecutive days directly to the vulva and massaged in gently.

### **TERAZOL 3 DUAL-PAK terconazole 80 mg ovule/0.8% vaginal cream Package**

One TERAZOL 3 Vaginal Ovule (80 mg of terconazole) is administered intravaginally once daily at bedtime for three consecutive days. In addition, a thin layer of TERAZOL 3 Vaginal Cream (0.8% terconazole) is applied for three consecutive days directly to the vulva and massaged in gently.

Before prescribing another course of TERAZOL therapy, the diagnosis of monilial infection should be confirmed by microscopic examination of a KOH smear and/or by culture.

Intractable candidiasis may be the presenting symptom of unrecognized diabetes mellitus. In these cases, appropriate diagnostic tests for diabetes should be done.

The therapeutic effect of TERAZOL products is not affected by oral contraceptive usage or menstruation.

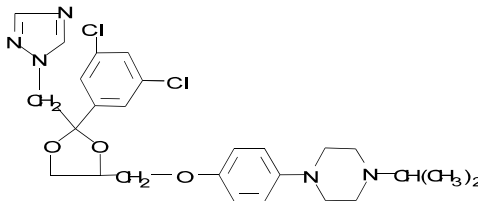
### **PHARMACEUTICAL INFORMATION**

**i) Drug Substance:**

Common Name: Terconazole

Chemical Name: cis-1-[4-[[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-4-(1-(methylethyl) piperazine

Structural Formula:



Molecular Formula:  $C_{26}H_{31}Cl_2N_5O_3$

Molecular Weight: 532.47

- Physical Form:** Terconazole, a triazole derivative, is a white to almost-white powder.
- Solubility:** Insoluble in water; sparingly soluble in ethanol and soluble in butanol.
- pH and pKa:** Terconazole is a weak base with three protonation sites as determined from non-aqueous titration. Only the monocationic form is titratable in aqueous medium. Terconazole pKa's are  $pK_{a1} < 1.5$ ,  $pK_{a2} < 1.5$ ,  $pK_{a3} = 8.4$ .
- Partition Coefficient:** The partition coefficient is  $\log P = 3.51$  (Octanol/Water).
- Melting Point:** The melting range is  $126^{\circ}\text{C} - 129^{\circ}\text{C}$ .

**ii) Composition:**

TERAZOL 3 terconazole 80 mg Vaginal Ovules are white to off-white ovules for intravaginal administration containing 80 mg of the antifungal agent terconazole, in a base of hydrogenated vegetable oils and butylated hydroxyanisole.

TERAZOL 7 terconazole 0.4% Vaginal Cream is a white to off-white, water-washable cream for intravaginal administration containing 0.4% of the antifungal agent terconazole. Propylene glycol is the antimicrobial agent used as a preservative and butylated hydroxyanisole is present as an antioxidant. Other nonmedicinal ingredients are cetyl alcohol, isopropyl myristate, polysorbate 60, polysorbate 80, purified water and stearyl alcohol.

TERAZOL 3 terconazole 0.8% Vaginal Cream is a white to off-white, water-washable cream for intravaginal administration containing 0.8% of the antifungal agent terconazole. Propylene glycol is the antimicrobial agent used as a preservative and butylated hydroxyanisole is present as an antioxidant. Other nonmedicinal ingredients are cetyl alcohol, isopropyl myristate, polysorbate 60, polysorbate 80, purified water and stearyl alcohol.

**iii) Stability and Storage Recommendations:**

TERAZOL 3 Vaginal Ovules, TERAZOL 7 Vaginal Cream and TERAZOL 3 Vaginal Cream should be stored at controlled room temperature (15°C-30°C).

**AVAILABILITY OF DOSAGE FORMS**

TERAZOL 3 terconazole 80 mg Vaginal Ovules are available as 2.5 g elliptically shaped white to off-white ovules. Each package contains three ovules and an ORTHO\* Vaginal Applicator.

TERAZOL 7 terconazole 0.4% Vaginal Cream is available in 45 g tubes with an ORTHO\* Vaginal Applicator.

TERAZOL 3 terconazole 0.8% Vaginal Cream is available in 20 g tubes with an ORTHO\* Vaginal Applicator.

TERAZOL 3 DUAL-PAK Package - Each package contains three TERAZOL 3 terconazole 80 mg Vaginal Ovules, an ORTHO\* Vaginal Applicator and a 9 g tube of TERAZOL 3 terconazole 0.8% Vaginal Cream.

**INFORMATION FOR THE CONSUMER****TERAZOL\* 3 DUAL-PAK\* Package****Patient Information**

TERAZOL\* 3 DUAL-PAK\* Package contains three TERAZOL\* 3 Vaginal Ovules (80 mg terconazole) and a 9 g tube of TERAZOL\* 3 Vaginal Cream (0.8% terconazole).

TERAZOL 3 DUAL-PAK Package has been prescribed to you for the local treatment of vulvovaginal candidiasis (moniliasis) and should only be used under medical supervision.

**Do not use this medication if you have already taken any products containing terconazole and have developed an allergy or intolerance to it.**

**This medication should not be used in the first trimester of pregnancy. If you are pregnant or think you are pregnant, consult your physician before using this medication.**

**PROPER USE OF THIS MEDICINE**

Use only as specifically directed. Do not alter the dosage or frequency of application unless ordered to do so by your physician.

This medicine was prescribed to treat your specific medical problem and is for your use only. Do not share it with others.

Complete the prescribed course of treatment to reduce the chance of re-infection.

Avoid tight-fitting undergarments, pants, pantyhose, etc.

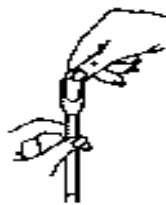
Keep all medicines out of the reach of children.

**PLEASE NOTE: TERAZOL 3 Vaginal Ovules affect natural rubber and must not be used with products such as condoms or diaphragms.**

**DOSAGE AND DIRECTIONS FOR USE: Both the ovules and cream should be used once daily at bedtime for 3 consecutive days.**

*Insertion of ovule:*

- ◆ Remove one ovule from the package. Place ovule in the receptacle of applicator as shown. The unit is now ready for insertion.



- ◆ Hold the filled applicator by the cylinder and gently insert it into the vagina as far as it will go comfortably. Press the plunger and deposit ovule. While keeping the plunger depressed, remove the applicator from the vagina.

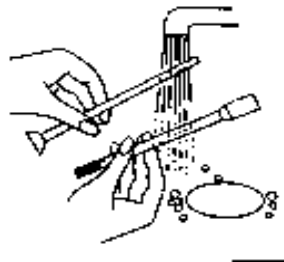


*Following insertion of the ovule:*

- ◆ Rub a thin layer of cream directly onto the vulva for 3 consecutive days.

*Care of applicator:*

- ◆ After each use, clean the applicator: hold the cylinder of the applicator with one hand and remove the plunger with the other hand by pulling in the opposite direction. Wash with soap and warm water. To reassemble, gently push the plunger back into the cylinder as far as it will go.



## **SIDE EFFECTS**

Along with its intended action, any medication may cause unwanted effects. Some of the side effects that have been reported include:

- ◆ headache, burning, pain, itching and irritation.

Should you experience these or any other side effects contact your doctor.

**If you need any further information, ask your physician or your pharmacist.**

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19 Green Belt Dr.  
Toronto, Ontario M3C 1L9

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## MYCOLOGY

### Antimycotic Activity (*In Vitro*)

*In vitro* terconazole effectively inhibits the growth of yeasts and other fungi including dimorphic and filamentous species. The potency of terconazole varies not only with the species tested, but also with the conditions under which the yeast or other fungus is grown.

Yeast grown in medium favoring mycelium formation are particularly sensitive to terconazole. In addition, the pH and nutrient content of the media, as well as the presence of serum in the medium and the ambient temperature, all affect the *in vitro* potency of terconazole. While it is difficult to precisely define the *in vitro* antifungal potency of terconazole, it does demonstrate a broad spectrum of antimycotic activity (Table I).

Antifungal activity also has been demonstrated against *C. tropicalis*, *C. krusei*, *Trichophyton rubrum*, *T. mentagrophytes*, *Cryptococcus neoformans*, *Torulopsis glabrata* and other yeasts and fungi.

The MIC values for terconazole against most species of lactic acid bacteria were  $\geq 128$  mcg/mL. Therefore, these beneficial bacteria are not affected by drug treatment.

The effects of terconazole on yeast have been observed via the electron microscope. At concentrations as low as  $10^{-8}$ M (5.3 ng/mL), terconazole begins to affect yeast morphology, as manifested by the appearance of dense lipophilic bodies along the cell membrane and inhibition of mycelia formation. At  $10^{-6}$ M terconazole, degenerative changes in yeast cell morphology are present, leading to complete necrosis.

TABLE I

## IN VITRO ANTIFUNGAL ACTIVITY OF TERCONAZOLE (SABOURAUD GROWTH MEDIUM)

(from Van Cutsem et al., Chemotherapy 29:322. 1983)

	Number of Strains	100 mg/mL			10 mg/mL			1 mg/mL			0.1 mg/mL		
		A†	B†	C†	A†	B†	C†	A†	B†	C†	A†	B†	C†
<i>Microsporum canis</i>	4	4				4			4				4
<i>M. audouini</i>	5	5				5			5				5
<i>Trichophyton rubrum</i>	48	48			48			16	32		4		
<i>T. mentagrophytes</i>	14	14			1	13		1	13				14
<i>T. tonsurans</i>	2	2			2				2				2
<i>T. verrucosum</i>	4	4			4			1	3				4
<i>Keratinomyces aielloi</i>	1	1			1				1				1
<i>Epidermophyton floccosum</i>	1	1			1			1	10		1		21
<i>Candida albicans</i>	27	22	5		5	10	12	2	15		6		
<i>C. tropicalis</i>	2	2			1		1	1	1				2
<i>C. krusei</i>	3	3			3				3				3
<i>Torulopsis glabrata</i>	2	1	1				2		2				2
<i>Cryptococcus neoformans</i>	5	5			5			2	3				5
<i>Trichosporon cutaneum</i>	1	1					1		1				1
<i>Sporothrix schenckii</i>	2	2					2		2				2
<i>Scopulariopsis brevicaulis</i>	2	2					2		2				2
<i>Allescheria boydii</i>	4	4			4				4				4
<i>Monosporium apiospermum</i>	1	1			1				1				1
<i>Ascosphaera apis</i>	3	3			3				3				3
<i>Phialophora verrucosa</i>	1	1			1				1				1
<i>Cladosporium carrionii</i>	1	1			1			1			1		1
<i>Cladosporium sp.</i>	1	1			1				1				1
<i>Aspergillus fumigatus</i>	10	2		8		10			10				10
<i>Saprolegnia sp.</i>	1	1			1				1				1
<i>Mucor sp.</i>	3	1	1	1	1	2			3				3
<i>Rhizopus sp.</i>	2			2		2			2				2
<i>Absidia ramosa</i>	1		1			1			1				1
<i>Pythium ultimum</i>	1	1				1			1				1
<i>Basidiobolus meristosporus</i>	1	1			1				1				1

†A: complete inhibition after 2 weeks of exposure

†B: marked inhibition

†C: no marked inhibition

## Assessment of Resistance:

Using a range of *Candida* species and dermatophytic fungi in a standard, classical test for emergence of resistance to an antifungal compound, it has been concluded that resistance of fungi to terconazole should not occur during the agent's clinical use. No resistance to terconazole has developed during successive passages of *C. albicans*.

**In Vivo Protection Studies**

When applied intravaginally in the rat (Table II), cures of 50% of the animals or more are observed with terconazole concentration doses of 0.25% or more.

**TABLE II**  
**TOPICAL TREATMENT WITH TERCONAZOLE OF RAT VAGINAL CANDIDOSIS**  
(from Van Cutsem et al., Chemotherapy 29:322. 1983)

Treatment	<u>Prophylactic Regimen</u>			<u>Therapeutic Regimen</u>		
	A <sup>a</sup>	B <sup>a</sup>	C <sup>a</sup>	A	B	C
Control (no treatment)	0/43 <sup>b</sup>	0/43	43/43	<sup>c</sup>	-	-
Placebo (vehicle)	0/50	1/50	49/50	0/124	1/124	123/124
Terconazole @ 0.063%	-	-	-	2/24	1/24	21/24
0.125%	14/18	0/18	4/18	12/46	2/46	32/46
0.25%	9/14	2/14	3/14	24/48	10/48	14/48
0.5%	11/12	1/12	0/12	35/48	2/48	11/48
1.0%	<sup>c</sup>	-	-	31/32	0/32	1/32
2.0%	-	-	-	8/8	0/8	0/8

<sup>a</sup> A = cured

B = marked improvement

C = not improved or cured

<sup>b</sup> data are presented as the number of animals cured, improved or not cured over the number of animals tested

<sup>c</sup> no data

**PHARMACOLOGY****Animal**

Pharmacologic Activity:

Studies performed in mice, rats and dogs determined that terconazole has no intrinsic secondary pharmacologic activity (Table III).

TABLE III  
PHARMACOLOGY STUDIES -- TERCONAZOLE

Species	Type of Test(s)	Dose & Route of Administration	Conclusion
Mouse	Neuropharmacology screening battery	40 mg/kg Subcutaneous (Vehicle 20% PEG 200)	Terconazole has no central nervous system or autonomic activity.
Rat	Neuropharmacology screening battery	40 mg/kg Intraperitoneal (Vehicle 20% PEG 200)	Terconazole has no central nervous system or autonomic activity.
Dog	Cardiac and hemodynamic activity in anesthetized animals	0.04 - 10 mg/kg Intravenous (Vehicle dist. H <sub>2</sub> O acidified with tartaric acid)	No significant effects predicted in clinical use.
Dog	Cardiac, hemodynamic, and behavioral activity in conscious animals.	10 mg/kg Oral (Vehicle dist. H <sub>2</sub> O, acidified with tartaric acid)	No significant effects predicted in clinical use.

## Pharmacokinetics:

Terconazole is readily absorbed following oral or subcutaneous administration (dog and rat), and slowly and poorly absorbed following vaginal (dog, rat and rabbit) or dermal (rabbit) administration.

Following oral or subcutaneous administration (dog and rat), the amount of terconazole absorbed increased with increasing administered dose. In the dog (above 5 mg/kg oral), the increase in the amount of terconazole absorbed into the systemic circulation was disproportionately greater than the increment in administered doses. The disproportionality was not observed for rat, rabbit or man (Table IV).

TABLE IV  
COMPARATIVE PEAK PLASMA TERCONAZOLE CONCENTRATIONS

Species	Dose	Route of Administration	Mean Peak Plasma Terconazole Concentration (ng/mL)
Rat	40 mg/kg	Intraperitoneal	---
	20 mg/kg	Oral	284 - 336
	5 mg/kg	Subcutaneous	323 - 537
Dog	10 mg/kg	Oral	1,294
	2.9 mg/kg	Intravenous	1,023 - 1,307
Rabbit	16 - 26 mg/kg	Intravaginal	100 - 195
	2 mg/kg	Dermal	6.44 (Day 3)
	4 mg/kg	Dermal	6.53 (Day 3)
	8 mg/kg	Dermal	23.6 (Day 3)
Human Female	20 mg as 0.4% Vaginal Cream	Intravaginal	4
	80 mg Suppository	Intravaginal	10
	240 mg Suppository	Intravaginal	26

Terconazole is highly bound ( $\geq 95\%$ ) to plasma proteins in blood *in vitro* (rat, dog and man). Following oral (4-6, 10 or 20 mg/kg) or subcutaneous (5 or 10 mg/kg) administration of radiolabeled terconazole to rats, radioactivity is extensively distributed to body tissues with the highest amounts occurring primarily in the well-perfused organs. The

rate of decline (of terconazole-related radioactivity) from tissues examined was similar to that in blood, suggesting no usual accumulation of parent compound and/or metabolites in any particular tissue.

In a dermal study in rabbits, plasma terconazole levels were below 2.5 ng/mL at all three dosage levels. However, on Day 3, the average plasma terconazole levels 2 hours after treatment (at doses of 2, 4 and 8 mg/kg, respectively) were 6.44, 6.53 and 23.6 ng/mL. In spite of repeated applications on subsequent days, levels did not change significantly from Day 3.

Terconazole is readily eliminated in the rat (5 mg/kg oral or subcutaneous) and does not accumulate following multiple dose oral administration of 5.0 or 20 mg/kg in the rat and 16-26 mg/kg (10 day) intravaginal administration in the rabbit.

In the dog, the pharmacokinetics of terconazole are both dose- and time-dependent, and terconazole does accumulate following multiple dose administration (5, 10 or 15 mg/kg for 13 weeks). This was not found in humans.

Terconazole is rapidly and extensively metabolized (rat, dog and human) with the metabolites, due primarily to oxidative N- and O-dealkylation, conjugation and dioxolane ring cleavage, being slowly eliminated by biliary/fecal and renal pathways.

Thus, the major metabolic reactions involved in the biotransformation of terconazole in animals and humans appear to be similar.

### **Human**

#### Pharmacokinetics:

Following oral (30 mg) administration of <sup>14</sup>C-labelled terconazole, the half-life of elimination from the blood for the parent terconazole was 6.9 hours (range 4.0-11.3). Terconazole is extensively metabolized; both the C<sub>max</sub> and AUC for unchanged terconazole represented a very small fraction (2.1% and 0.6%, respectively) of the corresponding C<sub>max</sub> and AUC for total radioactivity, suggesting rapid conversion of terconazole to metabolites. Total radioactivity from an oral

dose was eliminated from the blood with a half-life of 52.2 hours (range 44-60). Excretion of radioactivity was both by renal (32-56%) and fecal (47-52%) routes.

The absorption characteristics of terconazole 0.8% vaginal cream in pregnant or non-pregnant patients with vulvovaginal candidiasis were similar to those found in normal volunteers. Terconazole is not expected to affect the activity of hepatic drug metabolizing enzymes following therapeutic administration. Antimycotic concentrations of terconazole persist in the vagina for at least two days following therapy.

**TOXICOLOGY****Acute Toxicity:**

<u>Species</u>	<u>No. of Animals/ Group</u>	<u>Route</u>	<u>Dose Levels mg/kg</u>	<u>LD<sub>50</sub> mg/kg</u>
<u>Rat</u>				
Male	10	Oral	0, 160, 320, 640, 1280, 2560	1741
Female	10	Oral	0, 160, 320, 640, 1280, 2560	849.3
Male	10	Subcutaneous	0, 640	≥640
Female	10	Subcutaneous	0, 640	≥640
<u>Dog</u>				
Male	4	Oral	160, 320, 640, 1280	1280
Female	4	Oral	160, 320, 640, 1280	≥640
Male	4	Subcutaneous	40, 80, 160	97.8
Female	4	Subcutaneous	40, 80, 160	113

No lethality or systemic toxicity was observed following oral administration of 5 g/kg of terconazole 0.4% or 2% cream formulations. Formulation-dependent local irritation was observed following dermal applications of the 5% cream and 2% lotion formulation.

**Subchronic Toxicity:**

Intravenous administration for up to 28 days of terconazole 0.4% cream (sham control, untreated control: 0, 0.04, 0.12 or 0.20 mg/kg/day; 10 females/group) revealed no drug-related effects in rats. Only a local inflammatory response was observed in rabbits following intravaginal administration of 0.4% cream formulation (sham control, untreated control: 0, 0.04, 0.4, 0.12, 0.20 mg/kg/day; 6/group) and 0.8% cream formulation (sham control: 0, 2.0 mg/kg/day; 6/group).

In multidose dermal studies with rats and rabbits, the only toxicological finding was dose-dependent local irritation. Table V summarizes these studies.

TABLE V

STUDY ANIMALS	ROUTE	DURATION (WEEKS)	AVERAGE DOSE LEVELS TERCONAZOLE MG/KG/DAY	RESULTS (SEVERITY)
Rat 15/Sex/Group	Topical 2% Cream Formulation	6 (Treatment) 4 (Recovery)	0, 80, 400 or 2000	Local Irritation (Slight Erythema)
Rabbit 4/Sex/Group	Topical 0.4% Cream Formulation	4 (Treatment) 2 (Recovery)	0, 2, 4	Local Irritation Minimal
Rabbit 4/Sex/Group	Topical 2 or 5% Cream Formulation	13	2% Cream 5% Cream 0 8 16 20 40	Local Irritation Moderate

No systemic toxicity or vaginal irritation was observed in a 4 week multidose study with terconazole in a PEG suppository formulation, (vehicle control, sham control, 40 or 80 mg/kg/day; 6/group). Peak plasma levels of terconazole in rabbits ranged from 96-256 mg/mL over 28 days with no significant change in plasma levels.

Reddening of the vaginal mucosa was the only treatment related finding observed in a study with dogs receiving up to 16 mg/kg/day (160 mg suppository, vehicle control, sham control: 2 or 3/group) or 31.4 mg/kg/day of terconazole (Wecobee or PEG base suppository (4/group), vehicle control, sham control).

#### Chronic Toxicity:

In multidose studies, no systemic toxicity was observed following oral or subcutaneous administration of up to 8.7 mg/kg/day of terconazole for 3 months to rats. Minimum effects occurred at a dose of approximately 35-40 mg/kg/day (Table VI). Following oral or subcutaneous administration to dogs for 3 to 6 months there

was no systemic toxicity observed (3/sex/group in all dog studies: Oral; 0, 0.31, 1.25, 5.0 or 0, 5, 10, 15 mg/kg/day for 3 months. Subcutaneous; 0, 0.31, 1.25, 5 mg/kg/day for 6 months).

TABLE VI

<u>STRAIN/ SPECIES</u>	<u>MODE OF ADMIN.</u>	<u>NO./SEX/ GROUP</u>	<u>AVERAGE DOSE LEVELS MG/KG/DAY</u>	<u>STUDY DURATION (WEEKS)</u>	<u>RESULTS</u>
Wistar Rats	Oral	M - 20 F - 20	0, 2.14, 8.7, 35.9 0, 2.31, 9.4, 39.9	13	M and F: No systemic toxicity up to 8.7 mg/kg/day. No lethality. Decreased body weight gain.  F: Increased yellow pigment zona reticularis adrenal gland. Greater relative and absolute liver weights (12.9 g vs. 11.9 g, high dose vs. controls). Increased liver vacuolization, decreased lipid deposition in the glomerularis.
Wistar rats	S.C.	20	0, 2.5, 10, 40	13	M and F: No systemic toxicity. No treatment-related lethality. Increased spleen weight. Inflammatory reaction at injection site.  M: Decreased body weight gain (40 mg/kg/day)  F: Increased liver weight (40 mg/kg/day group)

Morbidity in a 3 month oral chronic study occurred in dogs receiving 15 mg/kg/day. Administration of 15/mg/kg/day was associated with decreased food consumption, decreased body weight gain, changes in hematologic and clinical pathology parameters and histopathic changes consistent with gastrointestinal bleeding, inanition and dehydration. At 15 mg/kg/day there was thyroid C cell hyperplasia in females and thymic atrophy in males. Only an increased evidence of diarrhea and emesis was associated with daily doses of 10 mg/kg/day of terconazole.

The onset of these toxicological effects may be in part explained by the results of drug plasma level studies. These studies have indicated that following oral and subcutaneous administration of terconazole in dogs, the amount of terconazole absorbed increases disproportionately to the increase in dose. Further, terconazole accumulates following multiple administration. In the 6 month subcutaneous chronic toxicity study there was no systemic toxicity or lethality. At 5 mg/kg/day there was an increase in leucocyte count and increased haptoglobin.

#### **Special Studies:**

In four standard 10 day rabbit vaginal irritation studies, terconazole as a 0.4% cream (1.0 mL/rabbit; 2 or 3/group), PEG or Wecobee base suppository formulation (1.0 mL/rabbit of 80 mg or 240 mg suppository; 2, 3 or 9/group) was acceptable. All studies included sham control, vehicle control and untreated control groups.

As evaluated by the Buehler method, terconazole 5% cream formulation (0.5 mL/animal; 40 guinea pigs; 5/sex/group) was not considered a contact sensitizer to guinea pigs. In studies conducted subsequent to results suggestive of photo reaction in clinical studies, terconazole was found to be a photoirritant, but not a photoallergen to guinea pigs (5 day topical application of 0.05 mL of 2% terconazole [induction] and of 0.05 mL 0.1% terconazole [elicitation] in 6 guinea pigs). Results of *in vitro* studies show that phototoxic reaction may not be detectable in the selected methodologies. In primary dermal irritation studies (6 male rabbits in each of three studies) the level of observed irritation was found to be formulation dependent. Moderate irritation was observed with both active and vehicle cream (0.5 mL of 5% terconazole) and lotion (0.5 mL of 2% terconazole, propylene glycol base formulations). Severe irritation with 0.5 mL of terconazole 2% tefose (mineral oil base formulations) was observed.

**Reproductive Studies:**

## General Fertility and Reproductive Performance:

No impairment of fertility occurred when rats were administered terconazole orally (0, 2.5, 10 or 40 mg/kg/day; 20/sex/group; treated animals mated to non-treated animals).

There was an increase in the fetal resorption rate and a decrease in litter size when only the males were orally dosed at 40 mg/kg/day.

## Teratology and Embryotoxicity:

There was no evidence of teratogenicity when terconazole was administered orally to rats throughout organogenesis at dosage levels up to 40 mg/kg/day (25 times the recommended intravaginal human dose for the ovules and 100 times that recommended for the cream) or subcutaneously at doses up to 20 mg/kg/day.

While these data indicate that terconazole does not show a teratogenic potential, there is evidence of embryotoxicity when the drug is given orally to animals.

When terconazole was administered to rats by gavage (vehicle control, 5, 10, or 20 mg/kg/day; 20/group) during the period of organogenesis a slight decrease in fetal weight, an increase in skeletal variants (incidence of shortened wavy ribs) and delayed ossifications occurred at 20-40 mg/kg/day. This alteration of skeletal ossification and the increase in skeletal variants at the highest dosage is considered to be secondary to the maternal toxicity or stress exhibited in the dams of this group by a reduction in body weight gain during most of the period of organogenesis.

Dosages at or below 10 mg/kg/day produced no embryotoxicity. The no-effect oral dose of 10 mg/kg/day resulted in a mean peak plasma level of terconazole in pregnant rats which exceeds by 44 times the mean peak plasma levels seen in normal subjects (0.004 mcg/mL) after intravaginal administration of terconazole. This assessment does not account

for possible exposure of the fetus through direct transfer of terconazole from irritated vagina to the fetus by diffusion across amniotic membranes.

Maternal stress was evident at the 20 mg/kg/day level. In dietary admixture studies where maternal stress was not evident, these effects were not seen at 40 mg/kg/day.

There was no evidence of teratogenicity in the offspring of rabbits treated orally with terconazole (0, 1.25, 5 or 20 mg/kg/day; gestation Days 6 through 15; 15/group). However, the data indicated a trend towards embryotoxicity at a dosage of 20 mg/kg/day (reduced percentage of pregnancies, increased resorptions, reduction in average pup weight) which may reflect the toxic effects resulting in loss of body weight in the dams.

#### **Perinatal and Post Natal Studies:**

There was no evidence of prolonged gestation or dystocia in rats administered terconazole orally from Day 16 of pregnancy through a 3 week lactation period (untreated, 2.5, 10 or 40 mg/kg/day; 20/group). It is concluded that terconazole does not adversely affect parturition.

Decreased pup weight gain and a decrease in pup survival were seen when terconazole was administered by gavage during the last third of gestation and continuing through weaning (4 and 40 mg/kg; 57 or 42/group). Pup weights were returned to normal range after the first week even though the dams continued to receive the drug.

In absorption, distribution, metabolism and excretion studies in which pregnant rats were orally or subcutaneously administered <sup>3</sup>H-terconazole, small amounts of terconazole-related radioactivity crossed the placenta and were found (1% of dose) in pooled fetuses.

The presence of terconazole in milk was not evaluated in nursing animals. Animal studies, however, have shown that

rat offspring exposed to terconazole via milk of dams treated orally with 40 mg/kg/day during lactation showed decreased survival through the first few days postpartum.

**Mutagenicity:**

Terconazole was not mutagenic when tested *in vitro* for induction of microbial point mutations (Ames test), chromosome aberration (human lymphocyte) or for inducing cellular transformation (BALB/3T3 cell culture) and *in vivo* for chromosome breaks (micronucleus test) or dominant lethal mutations in mouse germ cells.

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