PRODUCT MONOGRAPH

ECOSTATIN*

(econazole nitrate)

Topical Cream; 1%

Vaginal Ovules; 150 mg

Antifungal Agent

Bristol-Myers Squibb Canada
2365 Cote de Liesse
Montreal, Canada.
H4N 2M7

Date of Preparation:
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THERAPEUTIC CLASSIFICATION

Antifungal Agent

ACTION AND CLINICAL PHARMACOLOGY

Econazole nitrate exhibits antifungal activity against a wide variety of fungi, including dermatophytes, pathogenic yeasts, and moulds. Susceptible pathogenic organisms include *Candida albicans* and other *Candida* species, *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Epidermophyton floccosum*, and *Malassezia furfur*. It appears to act by altering the internal structure or cell membrane permeability of the fungus.

INDICATIONS

ECOSTATIN (econazole nitrate) Topical Cream is indicated for the treatment of infections caused by susceptible dermatophyte and *candida* species including *tinea pedis*, *tinea cruris*, *tinea corporis*, *tinea versicolor* and cutaneous candidiasis. It is not indicated for moderate or severe paronychia or onychomycosis.

ECOSTATIN Vaginal Ovules are indicated for the local treatment of vulvovaginal candidiasis (moniliasis).

CONTRAINDICATIONS

Hypersensitivity to econazole nitrate or any of the cream's or ovule's components.

ECOSTATIN Topical cream should not be used in or around the eyes.

PRECAUTIONS

If marked irritation or sensitization should occur during topical use or intravaginal use, discontinue ECOSTATIN (econazole nitrate) therapy.

Intractable candidiasis may be the presenting symptom of unrecognized diabetes. Appropriate urine/blood studies may be indicated in patients not responding to the treatment.

During treatment with ECOSTATIN Vaginal ovule, it may be advisable to instruct the patient to abstain from intercourse or alternatively, to recommend the use of a condom.

Pregnancy: Since econazole nitrate is absorbed in small amounts from the human vagina, it should not be used in the first trimester of pregnancy unless the physician considers it essential for the welfare of the patient.

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

ADVERSE REACTIONS

ECOSTATIN (econazole nitrate) is usually well tolerated. Adverse effects are limited to occasional local skin irritation manifested by erythema, pruritus, and burning or stinging sensation; cessation of therapy is rarely warranted.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

None known.

DOSAGE AND ADMINISTRATION

ECOSTATIN (econazole nitrate) Topical Cream

Apply twice daily, in the morning and evening. The cream should be massaged gently into the affected and surrounding skin areas.

Clinical improvement usually occurs promptly; however, complete disappearance of the symptoms of the disease may require prolonged treatment. Candida infections should be treated for at least two weeks and dermatophyte infections for one month to reduce the risk of recurrence. If no improvement has occurred after one month of treatment with ECOSTATIN Topical Cream, the diagnosis should be reassessed.

ECOSTATIN (econazole nitrate) Vaginal Ovules

For candidal vulvovaginitis, the recommended dose is one ovule inserted at bedtime for 3 consecutive days. The ovule should be inserted high into the vagina, by means of the applicator. The patient should be in the supine position while inserting the ovule.

It is important that therapy be continued during menstruation. Administration should be continued for the complete 3-day period even if the signs and symptoms of the disease disappear.

Although a 3-day course of therapy usually suffices, occasionally it may be necessary to institute a second course of therapy.

AVAILABILITY

ECOSTATIN Topical Cream provides 1.0% econazole nitrate formulated in a water-soluble cream base containing pegoxol-7- stearate, peglicol-5-oleate, mineral oil, butylated hydroxyanisole, benzoic acid, perfume, and purified water. Available in 15 g and 30 g tubes.

ECOSTATIN Vaginal Ovules are creamy-white to yellowish egg-shaped ovules each containing 150 mg econazole nitrate, formulated in a base of synthetic coconut oil triglycerides. Available in packages containing a reusable applicator and 3 ovules.

ECOSTATIN Combi-pack contains 3 ECOSTATIN Vaginal Ovules with applicator and ECOSTATIN Topical Cream, 1% in a 15 g tube.

Store at room temperature. Protect from heat. Do not refrigerate.

MICROBIOLOGY

In Vitro:

Several studies, using both tube-dilution and plate diffusion methods to test for fungistatic activity, confirm the broad spectrum antimycotic activity of econazole nitrate. Fungicidal activity against *Candida albicans* has also been demonstrated.

Minimum inhibitory concentrations (MIC's) of econazole nitrate against relevant organisms after 14 days incubation are as follows:

Organism	MIC (MCG/ML)
Aspergillus flavus	1.0
Aspergillus nidulans	1.0
Aspergillus fumigatus	1.0
Aspergillus niger	10.0
Candida albicans	100.0
Candida krusei	100.0
Candida parapsilosis	10.0
Candida pseudotropicalis	10.0
Candida stelloides	10.0
Candida tropicalis	100.0
Epidermophyton floccosum	0.01
Geotrichum candidum	100.0
Microsporum adouini	1.0
Microsporum canis	0.1 - 1.0
Microsporum gypseum	1.0
Mucor sp.	100.0
Rhodotorula sp.	100.0
Torulopsis glabrata	100.0
Trichophyton rubrum	0.1 - 1.0
Trichophyton mentagrophytes	0.01
Trichophyton interdigitale	1.0
Trichophyton verrucosum	0.1
Trichophyton violaceum	1.0
Trichophyton tonsurans	1.0
Trichophyton cutaneum	10.0

The following organisms have also been shown to be sensitive to econazole nitrate:

Fungi

(MIC's ranging from 0.01 to 100 mcg/mL)

Allescheria boydii
Alternaria sp.
Basidiobolus meristosporus
Blastomyces brasiliensis
Blastomyces dermatitidis
Cladosporium trichoides
Cladosporium wernackii
Cryptococcus neoformans
Ctenomyces mentagrophytes
Histoplasma capsulatum
Madurella grisea
Madurella mycetoma
Nocardia asteroides
Nocardia brasiliensis
Penicillium notatum
Rhizopus sp.
Saccharomyces cerevisiae
Saprolegnia sp.
Sporithrix schenkii
Streptomyces madurae
Streptomyces pelletieri
Streptomyces somaliensis

Bacteria

(MIC's ranging from 0.78 to 25 mcg/mL)

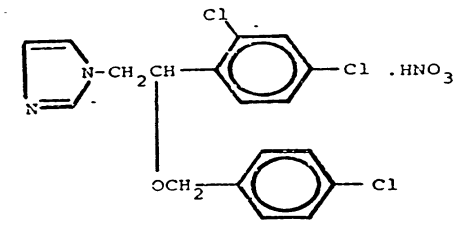
Bacillus anthracis
Bacillus mesentericus
Bacillus subtilis
Corynebacterium diphtheriae
Erysipclothrix insidiosa
Listeria monocytogenes
Staphylococcus aureus
Staphylococcus epidermidis
Staphylococcus hemolyticus
Streptococcus bovis
Streptococcus faecalis
Streptococcus faecium
Streptococcus pyrogenes

Econazole nitrate was found to be inactive against gram-negative bacteria.

PHARMACEUTICAL INFORMATION

CHEMISTRY

Structural Formula:



Molecular Formula: $C_{18}H_{15}Cl_3N_2O.HNO_3$

Molecular Weight: 444.72

Chemical Name: 1-[2-[(4-chlorophenyl)-methoxy]-2-(2,4-dichlorophenyl)ethyl]-1H-imidazole, nitrate salt.

Description: Econazole nitrate is a fine, white to off-white powder which is soluble in methanol and slightly soluble in ethanol, isopropanol, acetone, benzene and cyclohexane.

PHARMACOLOGY

ANIMAL PHARMACOLOLY

Pharmacokinetics

One gram of econazole-^{3}H nitrate topical cream (10 mg of econazole-^{3}H nitrate) was applied under occlusive dressing to the shaved backs of 2 groups of 6 female rabbits. The application site of one group was abraded.

An average of about 35% and 30% of the dose was absorbed through the abraded and unabraded skin, respectively. Percutaneous absorption was almost complete in 4 days with maximum levels of radioactivity present in plasma and tissues 24 hours after dosing in both groups. Absorption was found to occur mainly through the epidermis of hair follicles.

A cream formulation containing 5 mg of econazole nitrate (1.43-2.17 mg/kg) was administered intravaginally to rabbits. From 30 to 40% of the drug was found to be absorbed.

Miniaturized ovules delivering 0.96 or 2.48 mg/kg econazole nitrate were each administered intravaginally to one dog and vaginal absorption was estimated to be 0.87% and 1.10% respectively.

Dogs were intravaginally administered 1% or 2% cream formulations at doses of econazole nitrate of 10 mg/dog (1.01-1.28 mg/kg), 1 mg/kg and 2 mg/kg. Vaginal absorption was estimated at 27%, 12.4 - 15.2%, and 4.9% respectively.

Pharmacokinetics (cont'd):

Species	No. of animals	Dose (mg/kg)	Route of Administration	Excretion (%) Urine	Feces	Peak Plasma Concentration (mcg/ml)	Time to Attain Peak Plasma Levels (Hours)	Plasma t 1/2 (hours)* Alpha phase	Beta phase	Comments
Rat	12	10	Oral[1]	13	89	1.6	4	12	-	-
	12	10	I.V.[1]	18	68	6.8	0.5	13	-	
Rat	4	11.1	Oral[2]	9.7	78.5	2.6	4	7	53	83% of the oral dose appeared to have been absorbed.
	4	11.5	I.V.[2]	11.7	86.0	26	1	7	53	
Rat	6	20	Oral[3]	Males: 24.4	77.0	2.3% of dose	2	2	39	-
				Females: 17.3	87.7	1.3% of dose	4-8	-	37	
Rabbit	6	5.4	Oral[2]	29.8	57.6	1.4	8	14	63.5	I.V. profile indicates rapid distribution to extravascular compartment. 75% of oral dose was estimated to have been absorbed.
	6	5.3	I.V.[2]	39.6	46.4	3.2	0.5	13	66	
Dog	1 (2 tests)	5	Oral[2,4]	18.3	67.8	2.3, 2.6	2,24	25	25	Complicated plasma level pattern during 1st 24 hours indicative of redistribution of radioactivity into plasma; thereafter plasma level decreased in biphasic exponential manner.
	1 (2 tests)	5	I.V.[2,4]	11.8	75.5	3.56	0.0167 (1 min.)	25	25	
Monkey	1	4.9	Oral[2]	24.6	56.3	2.7	2	-	41	I.V. profile indicates rapid distribution to extravascular compartment; biexponential elimination. Oral doses subjected to metabolism during first passage through liver, although to a lesser extent after high dose.
	1	5.0	Oral[2]	33.5	52.7	1.4	4	-	41	
	1	51.5	Oral[5]	42.0	47.9	13.2	24	-	76	
	2 (2 tests each)	5.2-5.8	I.V.[2]	38.7	44.9	4.2	1	11.3	76	
Monkey	4	20	Oral[3]	Males: 58	26	1.5% of dose	4-8	21	-	Plasma elimination followed a mono-exponential pattern.
				Females: 47	37	1.5% of dose	4-8	21	-	

[1] 10% polyethylene-glycol solution
[2] ethanol-saline (1:4) solution
[3] 20% cremophor-water solution
[4] aqueous solution of 0.5% CMC and 0.04% Tween 80
[5] 15% agar suspension

*Alpha and Beta indicate that a biphasic exponential excretion pattern was observed.

HUMAN PHARMACOLOGY

Penetration of econazole-^{3}H nitrate cream, 1%, was studied in 4 human volunteers. Following application of 70-100 mg of cream, approximately 90% was found to remain on the skin surface, after periods ranging from 0.5-18 hours. Occlusion only slightly enhanced overall penetration. In the one subject whose application site was occluded, concentrations of 9.1%, 1.2% and 0.6% of the applied dose were found in the stratum corneum, epidermis and dermis, respectively, after 90 minutes. *In vitro* studies conducted on surgical specimens yielded similar results.

The site of application was occluded in a fifth subject for 16.5 hours. A total of 0.6% of the applied dose was excreted in the urine over 30.5 hours .

Ovules containing 50 or 150 mg ^{14}C-labelled econazole nitrate were administered intravaginally to female volunteers. Vaginal absorption was estimated at approximately 5%.

Serum concentrations obtained during the above study are given in the following table:

Mean Serum Econazole-^{14}C (ng/mL) After Administration of a Single 150 mg Ovule to 5 Normal Female Volunteers

Time (hours)	2	4	8	12	24	36	48	72	96	120	144	168
	0	0.9	6.1	10.5	39.3	62.3	64.9	59.9	48.8	37.9	28.5	24.7

Two other studies, each performed on healthy females treated intravaginally with single doses of a 1% cream formulation delivering aproximately 50 mg of econazole nitrate, resulted in 8.6% and less than 3% of the total amount of econazole nitrate being absorbed.

Miscellaneous studies

Doses of 10 or 40 mg/kg of econazole-^{14}C nitrate as a 0.2% suspension were orally administered to pregnant rats at various times during aestation. The drug was found to readily cross the placental barrier. The data suggest that in some instances, placental transfer was greater at the high dose than at the low dose. Placental transfer appeared to be greater during the later stages of pregnancy. Evidence of drug accumulation in the fetus was observed after multiple dosing.

Three groups of seven pregnant Charles River CD Sprague-Dawley rats were allowed to bear their young. Total doses of 10 or 40 mg/kg of radioactive econazole nitrate were administered orally in two equally divided doses to the dams on Days 2, 5 or 15 of lactation. Econazole nitrate and/or its metabolites were found to be readily excreted into the mothers' milk.

TOXICOLOGY

Acute Toxicity

Species	Sex	Formulation	Route	LD_{50} (mg/kg)
Mice	M/F	alcoholic solution	I.P.	50 (38 - 66)
Mice	M	1% suspension	I.P.	320 ± 20
Mice	M/F	alcoholic solution	Oral	205 (182 - 231)
Rats	M/F	alcoholic solution	Oral	365 (338 - 394)
Guinea pigs	M	aqueous suspension	Oral	272 (98 - 755)
Dogs	M/F	aqueous suspension	I.P.	217 (69 - 680)
Dogs	M	aqueous suspension	Oral	160

Signs of toxicity included dizziness, tonic and clonic spasms, slight cyanosis, ataxia, tremors, convulsions, sedation, diarrhea, loss of righting reflex and death.

A 54% concentration of econazole nitrate vaginal ovule, 50 mg or 150 mg in peanut oil was administered in single intraperitoneal doses of 2.7 to 21.6 g/kg of sample (doses of econazole nitrate ranging from 150-1200 mg/kg) to groups of 5, 9 or 10 female mice. There were no toxic signs on the day of dosing; however, some mice appeared to have diarrhea overnight. Transient weight losses were noted in some mice. Three of the 149 treated mice died.

Acute Interaction Studies

Acute toxicity interaction studies were conducted in mice given econazole nitrate intraperitoneally in combination with metronidazole, Ortho-Novum Tablet (norethindrone-mestranol, Ortho), tetracycline hydrochloride, and nitrofurantoin (administered orally), and nystatin, amphotericin B, nonoxynol-9, triamcinolone acetonide, Sultrin Cream (sulfathiazole, 3.42%, sulfacetamide, 2.86%, and sulfabenzamide, 3.7%, Ortho) (administered intraperitoneally). No evidence of toxicity potentiation was observed, except in the case of nonoxynol-9 where the combination resulted in LD50's eight times less than that observed for econazole nitrate alone.

Species	Sex	No. of Groups	No. of animals per group	Dose mg/kg/day	Duration of study	Route of Administration	Toxic Signs
Rat	Male Female	4 4	5 5	11.6, 23.2, 116.0 & control	3 weeks	Topical	High dose group: Desquamation of skin; mi hyperkeratoses in scarified & non-scarifi skin; slightly decreased basophilia of cytoplasm of liver cells.
Rabbit	Male Female	3 3	6,7,7 6,7,7	4, 12 & control 6 days/wk	6 weeks	Topical	All groups (including control): increase body weight gain and transient erythema more pronounced in dosed groups than cont epidermal hyperplasia; increase in thickn of application site.
Dog	Male Female	2 2	1 1	4, 12 & control (on other flanks) 6 days/wk	6 weeks	Topical	All groups (including control): transient erythema at application site; slight epic hyperplasia.
Dog	Male Female	2 2	1 1	1.6, 3.2, & control (on other flanks) 6 days/wk	6 weeks	Topical	High dose group: increase in BUN.
Rat	Male Female	5 5	6 6	10,40,80 or 160 & control	28 days	Oral	High dose group: slight leukopenia; increase SGPT, urea and alkaline phosphatase value fatty infiltration of liver cells; fatty degeneration of kidney epithelium; fatty atrophy of adrenals; poorly defined zona glomerulosa; fresh hemorrhages in lungs. 80 mg/kg dose: insignificant increase in absolute weight of livers; slight to mark swelling and decreased basophilia of live cells. 40 mg/kg dose group: slight swelling of l cells.
Monkey	Male Female	4 4	2 2	25,50 or 150 & control	30 days	Oral	High dose group: death (2 males); body we loss; increased liver weight (2 females); moderate to marked fatty infiltration of liver; possible myocardial fibrosis and nuclear variations of cardiac muscle fibr Mid & High Dose Groups: emesis; diarrhea
Monkey	Male Female	4 4	2 2	10,15 or 20 & control (not the same vehicle)	23 days	I.V.	All dosed groups: intravascular sclerosis perivascular soft tissue changes; hepatotoxicity; reduced overall cellularity of marrow; reduced number of megakaryocytes; local dermal and vascular reactions; faci and periocular edema (control did not con Cremophore EL thus no comparison possible All groups (including control with simila incidence): weight loss; hypertrophy of cardiac myofibers.
Rat	Male Female	4 4	15 15	1st week: 1, 3 or 10 & control Thereafter: 2,6 or 20 & control.	3 months	I.P.	High dose group only: 2 deaths; slight to marked increased total neutrophil counts males; slightly decreased mean hemoglobin hematocrit. High & Mid dose groups: slightly decrease mean body weight in males. All groups: dose-related palpable abdomin lesions.

Species	Sex	No. of Groups	No. of animals per group	Dose mg/kg/day	Duration of study	Route of Administration	Toxic Signs
Rabbit	Female	5	4	9.4 or 18.5 & 2 controls	3 weeks	Intra-vaginal (ovules)	No drug-related effects.
Dog	Female	4	3	13 or 18 & control	3 weeks	Intra-vaginal (ovules)	Slight increase in relative weights of pituitary, thyroid and adrenal glands in t dose group.
Dog	Male & Female	3	4	1, 3 or 10	4.5 weeks	I.P.	High dose group: decreased food consumptic sensitivity to palapation of abdomen; slig anemia; mild pulmonary inflammation. Mid & High dose groups: leukoblastic hyperplasia of bone marrow; leukocytosis; marked increase in serum GPT; slight to moderate increase in serum alkaline phosphatase.

Chronic Toxicity

Species	Sex	No. of Groups	No. of animals per group	Dose mg/kg/day	Duration of study	Route of Administration	Toxic Signs
Rat	Male Female	4 4	10 10	0.6, 1.8 or 6.0 & control	6 months	Topical	Increased alkaline phosphatase in one, two and three females of the low, mid - and high-dose groups, respectively.
Dog	Male Female	4 4	4 3	0.6, 1.8 or 6.0, & control	6 months	Topical	No drug-related effects.
Rat	Male Female	4 4	10 10	5,20 or 80 & control	6 months	Oral	Decreased food consumption and weight loss slightly increased urinary creatinine valu in males at 2 higher dose levels; slight increase in absolute heart weight of high-dose females; vacuolization of protoplasm hepatocytes in high dose group.
Rat	Male Female	4 4	10 10	45,135, 405 & control	3 months	Oral	High dose group only: Males - significant increase in urinary excretion of total protein; increased liver weight. Females - 2 deaths; increased kidney weight; increased urinary excretion of total protein. Both sexes - thickening of rumen and presence o dys- or hyperkeratosis of rumen. Mid & High dose groups: Males - decreased body weight gain. Females - increased urinary excretion of total protein, sodium and creatinine clearance. Mid dose group only: Slight microglobular steatosis at periphery of hepatic lobules. All treated groups: Increased serum alkali reserve, globulin level and alkaline phospl tase activity; dose related increase in wa intake and urine output; increased liver weight (females only).
Dog	Male Female	4 4	3 3	2.5,10, 40 & control	6 months	Oral	High dose group only: loss of body weight; low serum total protein, albumin, choleste rol, and sulphydryl groups; increased seru alkaline phosphatase; liver weight slightl increased. Mid & High dose groups: occasional tremor emesis. All treated groups: hepatocytic abnormali ties.
Dog	Male Female	3 3	3 3	15 or 45 & control	3 months	Oral	Increased serum alkaline phosphatase in hi dose group.
Rabbit	Female	8	4	0.2, 0.6 or 2.0 & control	6 months	Intra-vaginal (cream)	No drug-related effects.
Dog	Female	7	4	0.2, 0.6 or 2.0 control	6 months	Intra-vaginal (cream)	No drug-related effects.

Dermal Irritation Studies

Rats

Application of about 250 mg of econazole nitrate cream, 1%, under occlusive dressing, to the shaved and abraded backs of 4 male and 8 female rat, once daily for 5 days, produced no signs of irritation.

Rabbits

No signs of irritation were evident 24 and 72 hours after a single application of 0.5 g econazole nitrate to the abraded and unabraded backs of 6 albino rabbits.

Guinea Pigs

Five mL of a 1% suspension of econazole nitrate was applied to the skin of 20 guinea pigs 3 times a week for 3 weeks and then challenged 2 weeks later. No evidence of sensitizing (erythema) activity was noted. However, in the preliminary test, erythema was produced by 2% and 5% concentrations in 1 of 2 and 2 of 2 animals, respectively.

Human

Econazole nitrate cream, 1%, was applied to the skin of 100 patients with contact dermatitis due to known or unknown allergens, and occluded for 48 hours. Transient slight erythema and/or pruritus was produced in 6 patients.

In 45 patients who had shown positive reactions to substances other than econazole, econazole nitrate cream 3%, applied under occlusive dressing, caused reddening and/or edema at the application site in 5 patients.

Four of 75 patients with florid dermatoses exhibited reddening and/or edema after application of econazole nitrate cream, 3%. However, retesting of these 4 patients using econazole nitrate solution, 1%, did not result in any evidence of irritation. The initial reaction was therefore attributed to the cream base and/or to the higher concentration of econazole nitrate.

Econazole nitrate solution, 2%, applied to the healthy skin on the dorsum, soles, toes, and interdigital spaces of the feet of 6 female patients for 16 days, did not produce any signs of intolerance.

Vaginal Irritation

Dogs

Ovules containing 125 mg of econazole nitrate were inserted intravaginally into 3 adult female beagles twice daily for 5 consecutive days, and the vaginas subsequently examined grossly and histologically for signs of irritation. There was no evidence of vaginal irritation in any of these animals.

In another study, ovules containing 38 mg of econazole nitrate were inserted intravaginally into 8 adult female beagles twice daily for a period of 4 weeks. Under the conditions of the study, econazole nitrate ovule did not cause any irritation of the genital tract of female dogs.

Reproduction and Teratology:

Animal	Sex	No. of Groups	No. of animals per group	Dose mg/kg/day	Treatment Period	Route of Administration	Toxic Signs
Rat (Wistar)	Male Female	4 4	20 20	40,80,160 & control 40,80,160 & control	60 days prior to mating. 14 days prior to mating continuing to Day 21 of gestation	Oral	15% decrease in number of matings resulting in pregnancy; decreased number of implantations and live pu in high dose female-untreated male matings; mean duration of mating resulting in pregnancy delayed in treated male-untreated female matin No drug-related fetal abnormalities were detected.
Rat (Charles River CD Sprague-Dawley)	Male Female	4 4	12 24	20,50,125 & control 20,50,125 & control	10 weeks prior to mating. 2 weeks prior to mating, continuing to Day 13 in half the females, and through gestation to Day 21 of lactation in the other half	Oral	Increased pairing time required for mating; late fetotoxicity and reduc viability of offspring; reduction i number of implantation sites; increa in mean gestation time and occasion failure to deliver in high-dose fem groups.
Rat (Charles River CD)	Female	5	24	2,5,10, 50 & control	2 weeks prior to mating, continuing to Day 13 of gestation or Day 21 of parturition	Oral	50 mg/kg dose level: increased pre-implantation loss; decreased number of implantations. 10 & 50 mg/kg dose levels: increased gestat time and duration of labour; reduce viability of offspring at birth.
Mice (Swiss white)	Female	4	24,22 20,32	20,40,80 & control	Days 6-15 of gestation	Oral	No teratogenic changes in offspring at highest dose, increased number o deaths in utero and early resorptio
Rat (Wistar)	Female	4	20	40,80,160 & control	Days 6-15 of gestation	Oral	No effect on fetal development. No teratogenic changes in offspring.
Rabbit (New Zealand)	Female	3	20	40,80 & control	Days 6-15 of gestation	Oral	Death of dams due to pneumonia or enteritis. Decreased number of live fetuses and increased number of resorptions at high dose level. No teratogenic changes in offspring.
Rabbit (New Zealand White)	Female	4	15	0.5 g of 1,2 or 5% cream & control	Days 7-18 of gestation	Vaginal (cream)	No embryotoxicity, fetotoxicity or teratogenicity in offspring.
Rat (Wistar)	Female	4	20	40,80,160 & control	Days 16 of gestation through 21 of parturition	Oral	Decreases in litter size, survival rate and body-weight gain of offspring; increased number of still births.
Rat (Sprague-Dawley)	Female	4	31,25 25 & 24	10,20,40 & control	Days 15 of gestation through 21 of parturition	Oral	40 mg/kg dose only: reduced viabilit of offspring at birth and 4 days post-partum; shortened gestation periods.

Humans

ECOSTATIN Vaginal Ovules, 150 mg, were administered intravaginally to female volunteers once daily for 10 days. Vaginal cytology, clinical laboratory tests and daily vaginal examinations resulted in no significant findings. Subject diaries revealed that about two-thirds of the subjects receiving the drug (11 of 17) experienced mild irritation, usually transient in nature and more often associated with the vulva than with the vagina.

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