

NAME OF THE MEDICINAL PRODUCT

Tradename

PEVARYL[®]

Cream (econazole nitrate): PEVARYL[®]

Cutaneous spray solution (econazole nitrate): PEVARYL[®]

Powder (econazole nitrate): PEVARYL[®]

International Nonproprietary Names

econazole nitrate

Therapeutic Class

Topical dermatological anti-infective.

QUALITATIVE AND QUANTITATIVE COMPOSITION

PEVARYL[®] Cream, Spray solution and Powder contains 1% econazole nitrate

PHARMACEUTICAL FORM

Cream; Cutaneous spray solution; Powder.

CLINICAL PARTICULARS

Therapeutic Indications

PEVARYL[®] is indicated for:

- mycoses of the skin caused by dermatophytes, yeasts, or molds with or without accompanying gram positive bacterial infections;
- mycoses of the nails;
- Pityriasis versicolor.

Posology and Method of Administration

Adults

Cream, Spray Solution, Powder: Sufficient PEVARYL[®] should be applied once daily to cover affected areas for tinea pedis, tinea cruris, tinea corporis, and tinea versicolor; and twice daily for cutaneous candidiasis (once in the morning once in the evening). When moist, intertriginous spaces (e.g. spaces between the toes or the gluteal fold) should be wiped with gauze or bandages before applying PEVARYL[®]. For treatment of mycoses of the nails, an occlusive dressing is recommended. Early relief of symptoms is experienced by the majority of patients and clinical improvement may be seen fairly soon after treatment is begun; however, candida infections, tinea cruris and tinea corporis should be treated for two weeks and tinea pedis for one month in order to reduce the possibility of recurrence. If a patient shows no clinical improvement after the treatment period, the diagnosis should be re-determined. Patients with tinea versicolor usually exhibit clinical and mycological clearing after two weeks of treatment.

Children (2 to 16 years old)

The safety and effectiveness in children has not been established.

Elderly

Data are insufficient regarding the use of PEVARYL[®] in the elderly (>65 years old).

Contraindications

PEVARYL[®] is contraindicated in individuals who have shown hypersensitivity to any of its ingredients.

Special Warnings and Special Precautions for Use

For external use only. PEVARYL[®] is not for ophthalmic or oral use.

If a reaction suggesting sensitivity or chemical irritation should occur, use of the medication should be discontinued.

Econazole Nitrate Powder contains talc. Avoid inhalation of the powder to prevent irritation of airways, particularly in infants and children.

Interactions with Other Medicinal Products and Other Forms of Interaction

Econazole is a known inhibitor of CYP3A4/2C9. Due to the limited systemic availability after cutaneous application clinically relevant interactions are unlikely to occur, but have been reported with oral anticoagulants. In patients taking oral anticoagulants, such as warfarin or acenocoumarol, caution should be exercised and the anticoagulant effect should be monitored.

Pregnancy and Lactation

Pregnancy

In animal studies, econazole nitrate has shown no teratogenic effects but was foetotoxic in rodents at maternal subcutaneous doses of 20 mg/kg/day and at maternal oral doses of 10 mg/kg/day. The significance of this in humans is unknown.

Systemic absorption of econazole is low (< 10%) after topical application to the intact skin in humans. There are no adequate and well-controlled studies on adverse effects from the use of PEVARYL[®] in pregnant women, and no other relevant epidemiological data are available. No adverse effects of PEVARYL[®] on pregnancy or on the health of the foetus/newborn child have been identified from a limited number of post-marketing reports.

Because there is systemic absorption, PEVARYL[®] should not be used in the first trimester of pregnancy unless the physician considers it essential to the welfare of the patient.

PEVARYL[®] may be used during the second and third trimester if the potential benefit to the mother outweighs the possible risks to the foetus.

Lactation

Following oral administration of econazole nitrate to lactating rats, econazole and/or metabolites were excreted in milk and were found in nursing pups.

It is not known whether cutaneous administration of PEVARYL[®] could result in sufficient systemic absorption of econazole to produce detectable quantities in breast milk in humans.

Caution should be exercised when PEVARYL[®] is administered to nursing mothers.

Effects on Ability to Drive and Use Machines

None known.

Undesirable Effects

Clinical trial data

The safety of econazole nitrate cream (1%) and econazole nitrate emulsion (1%) was evaluated in 470 subjects who participated in 12 clinical trials and received at least one administration of either formulation. Adverse drug reactions (ADRs), as identified by the investigator, reported for $\geq 1\%$ of subjects treated with either econazole nitrate cream (1%) or econazole nitrate emulsion (1%) in these studies, are shown in Table 1.

Table 1: Adverse Drug Reactions Reported by $\geq 1\%$ of Subjects Treated with PEVARYL[®] Dermatological Formulations in 12 Clinical Trials

System Organ Class	%
Adverse Drug Reaction	(N=470)
Skin and Subcutaneous Tissue Disorders	
Pruritus	1.3
Skin burning sensation	1.3
General Disorders and Administration Site Conditions	
Pain	1.1

ADRs that occurred in $<1\%$ of subjects treated with either econazole nitrate cream (1%) or econazole nitrate emulsion (1%) in the 12 clinical trials are listed below in Table 2.

Table 2: Adverse Drug Reactions Reported by $<1\%$ of Subjects Treated with PEVARYL[®] Dermatological Formulations in 12 Clinical Trials

System Organ Class	
Adverse Drug Reaction	
Skin and Subcutaneous Tissue Disorders	
Erythema	
General Disorders and Administration Site Conditions	
Discomfort	
Swelling	

Post-marketing experience

Adverse drug reactions first identified during post-marketing experience with PEVARYL[®] Dermatological Formulations are included in Table 3. The frequencies are provided according to the following convention:

Very common	$\geq 1/10$
Common	$\geq 1/100$ and $< 1/10$
Uncommon	$\geq 1/1000$ and $< 1/100$
Rare	$\geq 1/10000$ and $< 1/1000$
Very rare	$< 1/10000$, including isolated reports.

In Table 3, ADRs are presented by frequency category based on spontaneous reporting rates.

Table 3: Adverse Drug Reactions Identified During Post-marketing Experience with PEVARYL[®] Dermatological Formulations by Frequency Category Estimated from Spontaneous Reporting Rates

Immune System Disorders	
<i>Very Rare</i>	Hypersensitivity
Skin and Subcutaneous Tissue Disorders	
<i>Very Rare</i>	Angioedema, Contact dermatitis, Rash, Urticaria, Blister, Skin exfoliation

Overdose

PEVARYL[®] is for cutaneous application only. In the event of accidental ingestion, treat symptomatically. If the product is accidentally applied to the eyes, wash with clean water or saline and seek medical attention if symptoms persist.

For ECONAZOLE NITRATE POWDER only:

Accidental inhalation of talc-containing powder: Massive accidental aspiration of Econazole Nitrate Powder may cause impaction blockage of airways, particularly in infants and children. Respiratory arrest should be treated with intensive supportive therapy and oxygen. If respiration is compromised, endotracheal intubation, removal of impacted material, and assisted breathing should be considered.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

A broad spectrum of antimycotic activity has been demonstrated against dermatophytes, yeasts and molds. A clinically relevant action against gram positive bacteria has also been found. Econazole nitrate acts by damaging cell membranes. The permeability of the fungal cell is increased. Subcellular membranes in the cytoplasm are damaged. The site of action is most probably the unsaturated fatty acid acyl moiety of membrane phospholipids.

Pharmacokinetic Properties

After topical application to the skin of normal subjects, systemic absorption of econazole nitrate is extremely low. Although most of the applied drug remains on the skin surface, drug concentrations were found in the stratum corneum which by far exceeded the minimum inhibitory concentration for dermatophytes. Inhibitory concentrations were achieved in the epidermis and as deep as the middle region of the dermis. Less than 1% of the applied dose was recovered in the urine and feces.

Preclinical Safety Data

Econazole nitrate has not been shown to be teratogenic when administered orally to mice, rabbits or rats. Longterm animal studies to determine carcinogenic potential were not performed.

PHARMACEUTICAL PARTICULARS

List of Excipients

Cream: PEG-6 (and) PEG-32 (and) glycol stearate, oleoyl macroglycerides, liquid paraffin high viscous, benzoic acid, butylated hydroxyanisole, purified water and flower perfume.

Spray Solution: ethanol, propylene glycol, flower perfume, tromethamol

Powder: precipitated silica, flower perfume, zinc oxide, talc.

Incompatibilities

None known.

Shelf-Life

Observe "expiry date" printed on outer pack.

Special Precautions for Storage

Cream: Store at or below 25°C.

Powder: Store at or below 25°C.

Cutaneous spray solution: Store at or below 30°C.

Keep PEVARYL[®] out of reach of children.

Nature and Contents of Container

Cream: 15 & 30 g

Cutaneous spray solution: 30 g

Powder: 30 g

Instructions for Use and Handling <and Disposal>

Not applicable.

MANUFACTURED BY

See outer carton.

DATE OF REVISION OF THE TEXT

May 2011