

# PEVARYL

Econazole nitrate

## Presentation

Pevaryl Cream: 1% w/w Pevaryl Foaming Solution: 1% w/w (as Econazole base) Pevaryl Powder: 1% w/w (not marketed) Pevaryl Solution: 1% w/w (not marketed)

## Uses

### Actions

Antifungal agent. Pharmacology *in vitro* activity: Econazole nitrate has antifungal activity against a wide range of yeasts and fungi including *Candida albicans*, *C.guilliermondi*, *Torulopsis* spp. and the dermatophytes, *Trichophyton rubrum*, *T.mentagrophytes*, *Epidermophyton*, *Malassezia furfur*.

**Mode of Action** PEVARYL appears to act by damaging the cell membrane and increasing its permeability. Synthesis of RNA is inhibited. Electron microscopy of *T. rubrum* shows changes in mitochondria (lysis of the cristae), degradation of the ribosomes and hypertrophy of the cytoplasmic membrane. In infections due to susceptible organisms cure rates of 80 to 90% were achieved. Average duration of treatment was 7 to 8 weeks although in some cases treatment had to be continued for longer periods.

### Pharmacokinetics

Dermal absorption has been studied using titrated drug. Dermal application produces a high concentration of econazole in the horny layer, which exceeds the MIC for most fungal species. The necessary MIC is also reached in the upper layers of the epidermis (within 100 minutes of application). A small quantity is absorbed. There is some binding to human plasma proteins but no appreciable binding to erythrocytes. The main routes for elimination are via urine and faeces.

### Indications

PEVARYL Cream, Solution and Powder are indicated for the treatment of dermatomycoses caused by dermatophytes (e.g. *Trichophyton rubrum*, *T. mentagrophytes*, *Epidermophyton floccosum*, *Malassezia furfur*) and yeasts (e.g. *Candida albicans*, *C. guilliermondi*, *Torulopsis* spp.).

PEVARYL Foaming Solution is indicated for the treatment of fungal skin infections and tinea.

## Dosage and Administration

PEVARYL Cream should be applied 2 to 3 times daily and rubbed gently with the finger. At the commencement of therapy the oozing intertriginous spaces should be kept dry, e.g. by means of gauze strips.

PEVARYL Solution should be applied 2 to 3 times daily. Avoid contact with the eyes, mucous membranes and genital region.

PEVARYL Powder can be used in combination with the cream or solution or used as a follow-up treatment to prevent recurrences. Application of PEVARYL Powder alone may be sufficient in cases such as impetigo. Continue the treatments until the skin lesions are completely healed.

PEVARYL Foaming Solution should be applied to the wet body on three consecutive evenings. The foam should not be rinsed off but allowed to dry. The drug should develop its effect during the nights and may be removed the next morning by washing it off. Should fungal skin infection and tinea not be cured after a period of two weeks the treatment must be repeated. Repeat the course 1 month and 3 months after initial treatment to prevent relapse.

## Contraindications

Although no specific contraindications are known, the product should not be used in patients known to be sensitive to any of the components.

## Warnings and Precautions

**Eyes** Avoid introduction of econazole cream, solution and powder into the eyes. Econazole solution should not be applied to mucosal membranes or the genital region. A short burning sensation may be experienced after the first application of the solution.

**Local irritation or hypersensitivity** Discontinue treatment if irritation or hypersensitivity occurs.

**Use in Lactation** It is not known whether econazole is excreted in breast milk or whether it has a harmful effect on the newborn. In rats given oral radio-labelled econazole, radio-activity was found in the milk at levels comparable to those in maternal blood. However, as systemic absorption is low in humans, any excretion into breast milk is likely to be low. However, no definite data concerning this are available.

**Lack of Response** If there is a lack of response to econazole, appropriate microbial studies should be carried out to confirm the diagnosis and rule out other pathogens. Intractable candidiasis may be the presenting symptom of unrecognised diabetes, thus appropriate urine/blood studies may be indicated in patients not responding to treatment.

Avoid contact with contraceptive diaphragms and this product since the rubber may be damaged by the preparation.

Overgrowth of non-susceptible organisms may occur with prolonged use of any topical antimicrobial agent, including econazole.

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

## Adverse Effects

In a series of 948 patients, side effects, mainly burning sensation and pruritus were reported by 2.8%. Treatment was discontinued in 9 patients. Some local irritation may be encountered in eczematous areas.

## Interactions

None known.

## Overdosage

No information is available concerning overdosage in humans as absorption and toxicity following topical application is low and no treatment should be necessary.

## Pharmaceutical Precautions

Nil.

## Medicine Classification

Pharmacy Only Medicine.

## Package Quantities

Pevaryl Cream = 20g Pevaryl Foaming Solution = 10ml sachets, 3s Pevaryl Powder = 10ml and 30ml (Not marketed) Pevaryl Solution = 30g. (Not marketed)

## Further Information

*In vitro* studies have demonstrated that econazole is effective against Gram-positive bacteria and Trichomonas species.

**Animal Pharmacology:** In rats and mice, oral econazole (40 mg/kg) has no parasympatholytic, parasympathomimetic, CNS stimulant; CNS depressant, analgesic, antiwrithing or toxic effects. *In vitro*, on isolated smooth muscle preparations and cardiac tissue, it is devoid of anticholinergic and antiserotonin activity, and alpha or beta adrenergic effect. A non-specific, non-competitive antispasmodic activity has been observed on guinea pig ileum. No inotropic effects were observed.

**Acute Toxicity:** Oral LD<sub>50</sub> in mice is 462 mg/kg, in rats 667 mg/kg and guinea pigs 272 mg/kg. LD<sub>50</sub> in the dog is 217 mg/kg when administered i.p.

**Chronic Toxicity:** Chronic (six month) toxicity has been studied in rats and dogs at doses up to 40 mg/kg (dog) and 60 mg/kg (rat). In rats slightly elevated creatinine values occurred in males dosed at 15 and 60 mg/kg. No signs of histological change were found in any group. In dogs autopsy findings revealed an increase in relative liver weight in the 40 mg/kg group. Histological changes in liver consisting of cloudy swelling, large vacuoles and hyaline deposits were seen at 10 and 40 mg/kg dose levels. Heart weights increased at 2.5 mg/kg dose levels.

**Teratology:** Econazole was administered to pregnant rats at doses of 40, 80, 160 mg/kg, & to pregnant rabbits at doses of 40 & 80 mg/kg. No teratogenic effects were produced in rat & rabbit fetuses. In various reproductive studies in female rats given oral doses of up to 40 mg/kg/day the following observations have been made at different dose levels: a decrease in pregnancy rate, an increase in the number of resorptions, an increase in the mean gestation time & reduced viability of the offspring at birth. With male rats an increase in the mating time necessary to achieve pregnancy was seen. In reproduction studies, rabbits given oral doses of up to 80 mg/kg/day, showed a dose related increase in resorption rate, & a decrease in average litter size was seen. However no effect on pregnancy rate was seen.

**Tolerance:** In the rabbit eye econazole provoked minor to moderate conjunctival responses which resolved within seven days. There is suggestive evidence from a study in 35 patients that econazole

nitrate when applied to the skin is unlikely to cause reactions of a phototoxic or photosensitising nature.

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## **Date of Preparation**

4 June 2010