NAME OF THE MEDICINAL PRODUCT

PEVISONE®

Cream: PEVISONE® CREAM

Ointment: PEVISONE® OINTMENT

International Nonproprietary names

Econazole nitrate, triamcinolone acetonide.

Therapeutic Class

Topical anti-infective, anti-inflammatory.

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram contains 10 mg econazole nitrate and 1 mg triamcinolone acetonide.

PHARMACEUTICAL FORM

Cream for cutaneous application to the skin.

CLINICAL PARTICULARS

Therapeutic Indications

PEVISONE Cream is indicated for the treatment of skin infections caused by dermatophytes or *Candida* spp., in which inflammatory symptoms are prominent.

Posology and Method of Administration

Adults

PEVISONE Cream should be applied sparingly to the skin lesion no more than 2 times daily, preferably once in the morning and once in the evening. PEVISONE Cream should not be applied with an occlusive dressing, nor to large areas of skin on the body.

The duration of treatment with the PEVISONE Cream should continue until the inflammatory symptoms subside but not longer than 2 weeks; after 2 weeks of therapy with PEVISONE Cream, continue therapy as needed with a preparation containing econazole or econazole nitrate alone.

Children (2 to 16 years old)

The safety and effectiveness in children has not been established.

Elderly

Data are insufficient regarding the use of PEVISONE in the elderly.

Pediatric Use

Pediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced HPA axis suppression and Cushing's syndrome than mature patients because of a larger skin surface area to body weight. Caution should be exercised.

Contraindications

PEVISONE Cream is contraindicated in individuals who have shown hypersensitivity to any of its ingredients.

Like any other dermatological preparation containing corticosteroids, PEVISONE Cream is contraindicated in specific skin conditions such as tuberculosis, varicella, herpes simplex or other viral infections of the skin, or fresh vaccination sites.

Special Warnings and Special Precautions for Use

For external use only. PEVISONE Cream is not for ophthalmic or oral use.

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

Corticosteroids applied to the skin can be absorbed in sufficient amounts to produce systemic effects, including adrenal suppression. Systemic absorption may be

increased by various factors such as application over a large skin surface area, application to damaged skin, application under occlusive skin dressings and prolonged duration of therapy.
Repeated application and/or prolonged application of topical corticosteroids in the periorbital region may induce cataracts, ocular hypertension, or increase the risk of glaucoma in patients.
Topical corticosteroids are associated with skin thinning and atrophy, striae, rosacea, perioral dermatitis, acne, telangiectasis, purpura, hypertrichosis, and delayed wound healing.
Topical corticosteroids may lead to increased risk of dermatological superinfection or opportunistic infection.

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

PEVISONE Cream

There are no adequate and well-controlled studies on adverse effects from the use of PEVISONE Cream in pregnant women, and no other relevant epidemiological data are available. No adverse effects on pregnancy or on the health of the foetus/newborn child have been identified from a limited number of post-marketing reports.
PEVISONE Cream should be used in the first trimester of pregnancy only when the physician considers it essential to the welfare of the patient. PEVISONE Cream may be used during the second and third trimester if the potential benefit to the mother outweighs the possible risks to the foetus. Drugs of this class should not be used extensively in large amounts, over large skin surface areas, or for a prolonged period of time in pregnant patients.
Studies in animals have shown reproductive toxicity [foetotoxicity with econazole and teratogencity for triamcinolone (see below)]. However, the risk in humans is unknown.

Econazole Nitrate

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 finding in humans is unknown. Systemic absorption of econazole is low (<10%) after topical application to the intact skin in humans.

Triamcinolone Acetonide

Triamcinolone (within the human therapeutic range and greater) has been associated with cleft palate in the offspring when given to pregnant mice, rats, rabbits and hamsters, and pulmonary hypoplasia in rats. In nonhuman primates, administration of triamcinolone (at doses <1 to 20 x clinical dose) has been associated with central nervous system effects, neural tube defects, craniofacial and skeletal abnormalities, and growth retardation. Limited data in the literature indicate that up to 5% of topically applied triamcinolone to the skin is systemically absorbed in humans.

Lactation

PEVISONE Cream

There are no adequate and well-controlled studies on the topical administration of PEVISONE Cream during lactation. It is not known whether concomitant topical administration of PEVISONE Cream to the skin could result in sufficient systemic absorption to produce detectable quantities in breast milk in humans. Caution should be exercised when PEVISONE Cream is administered to nursing mothers.

Econazole Nitrate

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 topical econazole nitrate could result in sufficient systemic absorption of econazole to produce detectable quantities in breast milk in humans.

Triamcinolone Acetonide

No studies in animals relevant to triamcinolone during lactation were identified. It is not known whether topical administration of triamcinolone to the skin could result in sufficient systemic absorption to produce detectable quantities in breast milk in humans.

Effects on Ability to Drive and Use Machines

None known.

Undesirable Effects

Clinical trial data

Adults

The safety of PEVISONE Cream [econazole nitrate (1%) plus triamcinolone acetonide (0.1%)] was evaluated in 182 adults who participated in 4 clinical trials. Adverse drug reactions (ADRs) that occurred in ≥1% of adults treated with PEVISONE Cream in these studies are listed below in Table 1.

Table 1: Adverse Drug Reactions Reported by ≥1% of Adults Treated with PEVISONE Cream in 4 Clinical Trials

System Organ Class	**%**
Adverse Drug Reaction	(N=182)
Skin and Subcutaneous Tissue Disorders	
Skin burning sensation	1.6
Skin irritation	1.6

No ADRs were reported in <1% of adults treated with PEVISONE Cream in the 4 clinical trials.

Children

The safety of PEVISONE Cream [econazole nitrate (1%) plus triamcinolone acetonide (0.1%)] was evaluated in 101 children (ages 3 months to 10 years) who participated in 1 clinical trial. ADRs reported for ≥1% of children treated with PEVISONE Cream in this study are shown in Table 2.

Table 2: Adverse Drug Reactions Reported by ≥1% of Children Treated with PEVISONE Cream in 1 Clinical Trial

System Organ Class	**%**
Adverse Drug Reaction	(N=101)
Skin and Subcutaneous Tissue Disorders	
Erythema	1.0

No ADRs were reported in <1% of children treated with PEVISONE Cream in the 1 clinical trial.

Post-marketing experience

Adverse drug reactions first identified during post-marketing experience with PEVISONE Cream are included in Table 3. The frequencies are provided according to the following convention:

Very common	≥1/10
Common	≥1/100 and < 1/10
Uncommon	≥1/1,000 and <1/100
Rare	≥1/10,000, <1/1,000
Very rare	<1/10,000, 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 PEVISONE Cream by Frequency Category Estimated from Spontaneous Reporting Rates

Immune System Disorders	
Very Rare	Hypersensitivity
Skin and Subcutaneous Tissue Disorders	
Very Rare	Angioedema, Contact dermatitis, Skin atrophy, Pruritus, Skin exfoliation, Skin striae, Telangiectasia, Erythema
General Disorders and Administration Site Conditions	
Very Rare	Application site pain, Application site swelling

Overdose

PEVISONE Cream is for cutaneous application only. Corticosteroids applied to the skin, including triamcinolone, can be absorbed in sufficient amounts to produce systemic effects.

In the event of accidental ingestion, treat symptomatically. If PEVISONE Cream is accidentally applied to the eyes, wash with clean water or saline and seek medical attention if symptoms persist.

PHARMACOLOGICAL PROPERTIES

Chemistry

Econazole nitrate isatriazole fungicide, designatedchemicallas 1-[2-[(4-chlorophenyl) methoxy]-2-(2,4-dichlorphenyl)ethyl]-,1H-imidazole mononitrate. The empirical formula is C18H15CI3N2O·HNO3. The molecular weight is 444.70. Econazole nitrate is a white to almost white crystalline powder. Econazole nitrate is soluble in methanol; sparingly soluble in methylene chloride; slightly soluble in alcohol;; very slightly soluble in water (0.05%). Triamcinolone acetonide is a fluorinated corticosteroid, designated chemically as 9-Fluoro-11beta, 16 alpha, 17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetyl with acetone. The empirical formula is C24H31FO6. The molecular weight is 434.51. Triamcinolone acetonide is a white or cream-colored, almost odorless fine crystalline powder. It is practically insoluble in water, sparingly soluble in alcohol, chloroform, or methyl alcohol, and slightly soluble in ether.

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. Sub-cellular membranes in the cytoplasm are damaged. The site of action is most probably the unsaturated fatty acid acyl moiety of membrane phospholipids. Triamcinolone acetonide is a more potent form of the naturally-occurring adrenocortical hormone. The mechanism of anti-inflammatory activity of the corticosteroids is unclear, but there is some evidence to suggest that a recognizable correlation exists between vasoconstrictor potency and therapeutic efficacy in man. The quantitative ratio of the two active principles of this drug product are such that each one of them can carry its own activity without inhibition by the other.

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. The extent of percutaneous absorption of topical corticosteroids is determined by many factors including vehicle, integrity of the epidermal barrier and the use of occlusive dressings. Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin increase percutaneous absorption.

Preclinical Safety Data

Econazole nitrate has not been shown to be teratogenic when administered orally to mice, rabbits or rats. Like other corticosteroids, triamcinolone acetonide has been shown to be teratogenic in rats and rabbits. Long-term animal studies to determine carcinogenic potential were not performed.

PHARMACEUTICAL PARTICULARS

List of Excipients

Cream: Benzoic acid, PEG-6 (and) PEG-32 (and) glycol stearate, oleoyl macrogolglycerides, paraffin oil, butylated hydroxyanisole, disodium edetate, purified water.

Ointment: White soft paraffin, Dehymuls E, isopropyl myristate, liquid paraffin, white beeswax, sodium phosphate, disodium edetate, benzoic acid, butylated hydroxyanisole, purified water, triamcinolone acetonide.

Incompatibilities

None known.

Shelf-Life

Observe “expiry date” printed on outer pack.

Special Precautions For Storage

Store at or below 25°C.

Keep out of reach of children.

Nature And Contents Of Container

Cream: 15, 30 & 100 g tubes.

Ointment: 15 g tubes.

Instructions for Use and Handling

Not applicable.

MANUFACTURED BY
See outer carton.

DATE OF REVISION OF THE TEXT
May 2011