GYNO-PEVARYL®

NAME OF THE MEDICINAL PRODUCT

Vaginal Cream: GYNO-PEVARYL®
50 mg Ovules: GYNO-PEVARYL® 50
150 mg Ovules: GYNO-PEVARYL® 150
150 mg Depot Ovules: GYNO-PEVARYL® DEPOT
Combination Packs Ovules and Cream: GYNO-PEVARYL® 150 (Combipack)

QUALITATIVE AND QUANTITATIVE COMPOSITION

Vaginal cream: 100 g of cream contains 1.00 g econazole nitrate.
50 mg Ovules: 1 ovule contains 50.0 mg econazole nitrate.
150 mg Ovules: 1 ovule contains 150.0 mg econazole nitrate.
150 mg Depot Ovules: 1 ovule contains 150.0 mg micronized econazole nitrate.
Combination Packs Ovules & Vaginal cream: 3 ovules plus 15g tube of 1% Vaginal cream.
For excipients, see List of Excipients.

PHARMACEUTICAL FORM

Vaginal Cream; Ovules of 50 or 150 mg; 150 mg Depot Ovules; combination pack of Ovules and Vaginal cream.

CLINICAL PARTICULARS

Therapeutic Indications

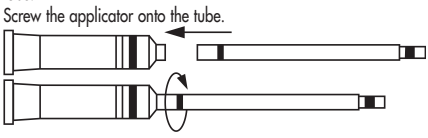
GYNO-PEVARYL® is indicated for the treatment of vulvovaginal mycoses and mycotic balanitis.

Posology and Method of Administration

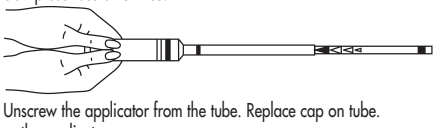
Adult Females
Vaginal cream: 1 applicator full (5 cc) is administered into the vagina once daily at bedtime for not less than 14 consecutive days. The treatment should be continued for the full course, even if the subjective symptoms (pruritus, leucorrhoea) disappear.
50 mg Ovules: One ovule is inserted high into the vagina once daily at bedtime for not less than 14 consecutive days. This is best done in the reclining position. The treatment should be continued for the full course even if the subjective symptoms (pruritus, leucorrhoea) disappear.
150 mg Ovules: One ovule is inserted high into the vagina once daily at bedtime for three consecutive days. This is best done in the reclining position. In event of relapse, or if the culture examination one week after treatment is positive, a second round of treatment should be undertaken.
150 mg Depot Ovules: One depot ovule is inserted high into the vagina in the morning and one in the evening. This is best done in the reclining position.
Combination Pack 150 mg Ovules & Vaginal cream: One ovule is inserted high into the vagina (this is best done in the reclining position) and a thin film of cream is applied over the vulval and anal areas once daily at bedtime for three consecutive days.
Males
Wash and dry the penis and then apply the cream to the glans and prepuce once a day for 14 consecutive days.
Children (2 to 16 years old)
The safety and effectiveness in children has not been established.
Elderly
Data are insufficient regarding the use of GYNO-PEVARYL® in the elderly (>65 years old).

Method of Administration

Cream:
Filling the applicator:
1. Remove the cap from the tube.
2. Use the pointed tip on the top of the cap to puncture the seal on the tube.
3. Screw the applicator onto the tube.



4. Squeeze the tube from the bottom and fill the applicator until the plunger stops. if the plunger shows resistance, pull gently. The applicator should be filled completely unless the practicing physician prescribes otherwise.



5. Unscrew the applicator from the tube. Replace cap on tube.

Using the applicator:
1. Lie on your back with your knees bent and spread out.
2. Holding the applicator by the end of the barrel, insert the filled applicator into the vagina as far as it will comfortably go.
3. Slowly press the plunger to release the cream into the vagina.
4. Remove the applicator from the vagina and throw it away (but not down the toilet).

Contraindications

Hypersensitivity to any component of the product.

Special Warnings and Special Precautions for Use

The concurrent use of latex condoms or diaphragms with vaginal antiinfective preparations may decrease the effectiveness of rubber contraceptive agents. Therefore products such as GYNO-PEVARYL® should not be used concurrently with a diaphragm or latex condom. Patients using spermicidal contraceptives should consult their physician since any local vaginal treatment may inactivate the spermicidal contraceptive. GYNO-PEVARYL® should not be used in conjunction with other internal or external treatment of the genitalia. If marked irritation or sensitivity occurs the treatment should be discontinued. Patients with sensitivity to imidazoles have also reported sensitivity to econazole nitrate. (Not for ophthalmic or oral use.)

Interactions with Other Medicinal Products and Other Forms of Interaction

Although not studied, based on the chemical similarity of econazole with other imidazole compounds, a theoretical potential for competitive interaction with compounds metabolized by CYP3A4/2C9 exists. Due to the limited systemic availability after vaginal application (see Pharmacokinetic Properties), clinically relevant interactions are unlikely to occur. In patients on oral anticoagulants, such as warfarin and acenocoumarol, caution should be exercised and monitoring of the anticoagulant effect should be considered.

Pregnancy and Lactation

Pregnancy
In animal studies, econazole nitrate showed no teratogenic effects but was fetotoxic at high doses (see Preclinical safety data). The significance of this in humans is unknown. Because there is vaginal absorption, GYNO-PEVARYL® should not be used in the first trimester of pregnancy unless the physician considers it essential to the welfare of the patient. GYNO-PEVARYL® may be used during the second and third trimester if the potential benefit outweighs the possible risks to the fetus.
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 econazole nitrate is excreted in human milk. Caution should be exercised when using GYNO-PEVARYL® if the patient is breast-feeding.

Effects on Ability to Drive and Use Machines

None known.

Undesirable Effects

The most frequently reported adverse events in clinical trials were application site reactions, such as burning and stinging sensations, pruritus, and erythema.
Based on post-marketing experience, the following adverse reactions have also been reported:
Skin and subcutaneous tissue disorders; general disorders and administration site conditions
Very rare (< 1/10000): Localized application site (mucocutaneous) reactions, such as erythema, rash, burning and pruritus.
Isolated reports of localized allergic reactions. Isolated reports of generalized allergic reactions, including angioedema and urticaria.

Overdose

Overdose with econazole nitrate has not been reported to date. In the event of accidental ingestion, nausea, vomiting and diarrhea may occur. If necessary treat symptomatically.

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. Sub-cellular membranes in the cytoplasm are damaged. The site of action is most probably the unsaturated fatty acid acyl moiety of membrane phospholipids.

Pharmacokinetic Properties

Econazole is poorly absorbed after vaginal or topical administration in humans. Maximal concentrations of econazole and/or its metabolites in plasma or serum were observed 1-2 days following administration and were approximately 20-40 ng/mL for the Vaginal cream, 15 ng/mL for the 50 mg Ovule, 65 ng/mL for the 150 mg Ovule, < 1 ng/mL for the 2% Dermal cream applied to intact skin and 20 ng/mL for the 2% Dermal cream applied to stripped skin. The percentage of applied econazole dose absorbed was found to be approximately 5-7% for the Vaginal cream, 5% for the 50 or 150 mg Ovule, 0.1% for the 2% Dermal cream applied to intact skin and 3.7% for the 2% Dermal cream applied to stripped skin.
Econazole and/or its metabolites in the systemic circulation are extensively bound (>98%) to serum proteins. Econazole is extensively metabolized by oxidation, deamination and/or O-dealkylation with the metabolites being eliminated by renal and fecal pathways.

Preclinical Safety Data

Econazole has been tested in a comprehensive battery of non-clinical safety studies. Acute toxicity studies indicate a wide margin of safety. In (sub) chronic toxicity studies at high doses (50 mg/kg/day) the liver was identified as a target organ with minimal toxicity and full recovery.
Results of econazole reproduction studies showed no effects on fertility or teratogenicity. Low neonatal survival and fetal toxicity was associated only with maternal toxicity. No significant topical toxicity, phototoxicity, local dermal irritation, vaginal irritation or sensitization was noted. Only mild ocular irritation was noted with a cream formulation. In various test systems either no or some limited genotoxicity effects (structural chromosomal deviations) have been shown. Based on an overall assessment of these data and the indicated route of administration, including the resulting minimal systemic exposure to econazole, there is little relevance for clinical use.
No studies on the carcinogenic potential have been conducted due to the short course of proposed clinical therapy and the absence of any significant potential of econazole to be genotoxic in a way that could lead to initiation or promotion of tumor formation.
In conclusion, preclinical effects were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

PHARMACEUTICAL PARTICULARS

List of Excipients

Vaginal cream: PEG-6 (and) PEG-32 (and) glycol stearate, oleoyl macrogolglycerides, butylhydroxyanisole, benzoic acid, purified water, liquid paraffin
50 mg Ovules: Hard Fat (Wecobee M, Wecobee FS)
150 mg Ovules: Hard Fat (Wecobee M, Wecobee FS)
150 mg Depot Ovules: polygel 371, silica colloidal anhydrous, Hard Fat (Witepsol H19 and Wecobee FS), stearyl heptanoate

Incompatibilities

None known.

Shelf Life

Observe "expiry date" (month/year) printed on outer pack.

Special Precautions for Storage

Vaginal cream: Do not store above 25°C.
50 mg Ovules: Do not store above 30°C.
150 mg Ovules: Do not store above 30°C.
150 mg Depot Ovules: Do not store above 30°C.
Keep out of reach of children.

Nature and Contents of Container

Vaginal cream: 78g aluminum tubes
50 mg Ovules: blister packs (molded) 15
150 mg Ovules: blister packs (molded) 3
150 mg Depot Ovules: blister packs (molded) 2
Combination Packs: 3 Ovules and 15g tube of 1% Vaginal cream

Instructions for Use and Handling <and Disposal>

Not applicable.

DATE OF REVISION OF THE TEXT

December 2007

JANSSEN-CILAG
Manufactured by: see outer pack
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