PRODUCT NAME

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)
(econazole nitrate)

DOSAGE FORMS AND STRENGTHS

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 mg micronized econazole nitrate.
Combination Packs: Ovules & Vaginal Cream
For excipients, see List of Excipients.

CLINICAL INFORMATION

Indications

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

Dosage and Administration

Dosage

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, leukorrhea) 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, leukorrhea) 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.

Special Populations

Pediatrics (2 to 16 years old)

The safety and effectiveness in children has not been established.

Elderly (older than 65 years old)

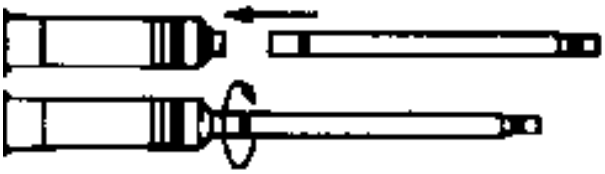
Data are insufficient regarding the use of GYNO-PEVARYL® in the elderly (>65 years old).

Administration

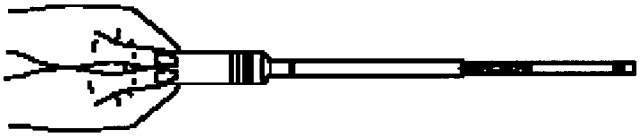
Cream:

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

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

Warnings and Precautions

For intravaginal use only. GYNO-PEVARYL® is not for ophthalmic or oral use.

The concurrent use of latex condoms or diaphragms with vaginal anti-infective 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.

Interactions

Econazole is a known inhibitor of CYP3A4/2C9. Due to the limited systemic availability after vaginal application (see *Pharmacokinetic Properties*), 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, Breast-feeding and Fertility

Pregnancy

Animal studies have shown reproductive toxicity (see Non-Clinical Information). 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 to the mother outweighs the possible risks to the fetus.

Breast-feeding

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.

Fertility

Results of econazole animal reproduction studies showed no effects on fertility (see Non-Clinical Information section).

Effects on Ability to Drive and Use Machines

None known.

Adverse Reactions

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of econazole nitrate based on the comprehensive assessment of the available adverse event information. A causal relationship with econazole nitrate cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Clinical trial data

The safety of GYNO-PEVARYL® Vaginal Cream and Vaginal Ovules was evaluated in 3630 patients who participated in 32 clinical trials. Adverse reactions reported for ≥1% of patients treated with either GYNO-PEVARYL® Vaginal Cream or Vaginal Ovules in these studies are shown in Table 1.

Table 1. Adverse Reactions Reported by ≥1% of Patients Treated with TRADENAME in 32 Clinical Trials

System Organ Class Adverse Reaction	TRADENAME % (N=3630)
Skin and Subcutaneous Tissue Disorders	
Skin burning sensation	1.2
Pruritus	1.2

Adverse reactions that occurred in <1% of patients treated with either GYNO-PEVARYL® Vaginal Cream or Vaginal Ovules in the 32 clinical trials are listed in Table 2.

Table 2. Adverse Reactions Reported by <1% of Patients Treated with GYNO-PEVARYL® in 32 Clinical Trials

System Organ Class Adverse Reaction
Skin and Subcutaneous Tissue Disorders
Rash
Reproductive System and Breast Disorders
Vulvovaginal burning sensation

Postmarketing data

In addition to the adverse reactions reported during clinical studies and listed above, the following adverse reactions have been reported during postmarketing experience (Table 3). The frequencies are provided according to the following convention:

Very common ≥1/10

Common ≥1/100 and <1/10

Uncommon ≥ 1/ 1000 and <1/100

Rare ≥1/10000 and <1/1000

Very rare <1/10000, including isolated reports.

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

Table 3. Adverse Reactions Identified During Post-marketing Experience with GYNO-PEVARYL® by Frequency Category Estimated from Spontaneous Reporting Rates

System Organ Class *Frequency category*	**Preferred Term**
Immune System Disorders	
Very Rare	Hypersensitivity
Skin and Subcutaneous Tissue Disorders	
Very Rare	Angioedema, Urticaria, Contact dermatitis, Skin exfoliation, Erythema
General Disorders and Administration Site Conditions	
Very Rare	Application site pain, Application site irritation, Application site swelling

Overdose

Symptoms and signs

Adverse events associated with overdose or misuse of GYNO-PEVARYL® are expected to be consistent with adverse reactions already listed in Adverse Reactions.

Treatment

GYNOPEVARYL® is for topical 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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Pharmacotherapeutic group: Antiinfectives and antiseptics, excl. combinations with corticosteroids, imidazole derivative, ATC code: G01A F05.

Mechanism of action

Econazole nitrate acts by damaging fungal cell membranes, resulting in increased permeability. Sub-cellular membranes in the cytoplasm are damaged. The site of action is most probably the unsaturated fatty acid acyl moiety of membrane phospholipids.

Pharmacodynamic effects

Microbiology

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.

Pharmacokinetic Properties

Absorption

Systemic absorption of econazole is extremely low after vaginal application. Following vaginal application of econazole nitrate cream, about 5% to 7% of the dose was absorbed. Mean peak plasma/serum concentrations of econazole and/or its metabolites were observed 1 to 2 days after

dose administration and were approximately 20 to 40 ng/mL for the Vaginal Cream, 15 ng/mL for the 50 mg Ovule, 65 ng/mL for the 150 mg Ovule.

Distribution

Econazole and/or its metabolites in the systemic circulation are extensively bound (>98%) to serum proteins.

Metabolism

Econazole that reaches the systemic circulation is extensively metabolized by oxidation of the imidazole ring, followed by O-dealkylation and glucuronidation.

Excretion

Econazole and metabolites are eliminated in urine and feces.

NON-CLINICAL INFORMATION

Preclinical effects were observed only at exposures considered sufficiently in excess of the maximum human exposure, indicating little relevance to clinical use.

Acute toxicity studies indicate a wide margin of safety with rodent oral LD50 values ranging from >160-463 mg/kg. In repeat dose toxicity studies, at high doses (50 mg/kg/day) the liver was identified as a target organ with minimal toxicity and full recovery.

Neither significant topical toxicity, phototoxicity, local dermal irritation, vaginal irritation nor sensitization was noted. Only mild ocular irritation was noted with a cream formulation.

Carcinogenicity and Mutagenicity

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 various test systems either no or some limited gene-toxicity 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.

Reproductive Toxicology

Results of econazole reproduction studies showed no effects on teratogenicity.

Fertility

Results of econazole reproduction studies showed no effects on fertility.

Pregnancy

Low neonatal survival and fetal toxicity was associated only with maternal toxicity. In animal studies, econazole nitrate has shown no teratogenic effects but was fetotoxic 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.

PHARMACEUTICAL INFORMATION

List of Excipients

Vaginal Cream: benzoic acid, butylhydroxyanisole, liquid paraffin, oleoyl macrogolglycerides, PEG-6 (and) PEG-32 (and) glycol stearate, purified water

50 mg Ovules: hard fat

150 mg Ovules: hard fat

150 mg Depot Ovules: Polygel 371, colloidal anhydrous silica, hard fat, stearyl heptanoate/caprylate

Incompatibilities

None known.

Shelf Life
See “expiry date” (month/year) printed on outer pack.
Storage Conditions
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.
See storage conditions on the outer pack.
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
Not applicable.
Instructions for Disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

MANUFACTURED BY
See outer carton.

DATE OF REVISION OF THE TEXT
21 March 2014