1. NAME OF THE MEDICINAL PRODUCT

GYNO-DAKTARIN 7 *CREAM VAGINAL*
Miconazole nitrate 20 mg/g cream

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram contains 20 mg of the active substance miconazole nitrate.

For excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

White, homogenous Cream for vulvar and vaginal use.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

Local treatment of vulvovaginal candidosis (monoliasis) and superinfections due to gram-positive bacteria(Streptococci and staphylococci).

4.2. Posology and Method of Administration

GYNO-DAKTARIN Cream

Once daily before bedtime, administer the contents of 1 applicator (about 5 g of cream) deeply into the vagina (see Section 6.6, Instructions for use and handling). Repeat this procedure for 7 days, even if symptoms (e.g. pruritus and leukorrhea) have disappeared or menstruation begins.

Treatment of concurrent symptoms of mycotic balanitis of the male partner: apply the cream twice daily on the glans penis. The treatment duration is the same as for the female partner.

4.3. Contraindications

GYNO-DAKTARIN Cream, is contraindicated in individuals with a known hypersensitivity to miconazole nitrate or another ingredient of the formulations.

4.4. Special Warnings and Special Precautions for Use

Should local sensitization or an allergic reaction occur, the treatment should be discontinued.

Appropriate therapy is indicated when the sexual partner is also infected.

GYNO-DAKTARIN products do not stain skin or clothes.

The concurrent use of latex condoms or diaphragms with vaginal anti-infective preparations may decrease the effectiveness of latex contraceptive agents. Therefore, GYNO-DAKTARIN products should not be used concurrently with a latex condom or latex diaphragm.

4.5. Interactions with Other Medicinal Products and Other Forms of Interaction

Miconazole administered systemically is known to inhibit CYP3A4/2C9. Due to the limited systemic availability after vaginal application, clinically relevant interactions occur very rarely. In patients on oral anticoagulants, such as warfarin, caution should be exercised and the anticoagulant effect should be monitored.

The effects and side effects of other drugs metabolized by CYP2C9 (e.g.,oral hypoglycemics and phenytoin) and CYP3A4 (e.g., HMG-CoA reductase inhibitors such as simvastatin and lovastatin and calcium channel blockers such as dihydropyridines and verapamil), when co-administered with miconazole, can be increased and caution should be exercised.

Contact should be avoided between latex products such as contraceptive diaphragms or condoms and GYNO-DAKTARIN since the constituents of GYNO-DAKTARIN may damage the latex (see Section 4.4, Special warnings and special precautions for use).

4.6. Pregnancy and Lactation

4.6.1. Use during pregnancy

Although intravaginal absorption is limited, GYNO-DAKTARIN Cream, should be used in the first trimester of pregnancy only if, in the judgement of the physician, the potential benefits outweigh the possible risks.

4.6.2. Use during lactation

It is not known whether miconazole nitrate is excreted in human milk. Caution should be exercised when using GYNO-DAKTARIN Cream, during lactation (see Section 4.5, Interactions with other medicinal products and other forms of interaction).

4.7. Effects on Ability to Drive and Use Machines

Not applicable.

4.8. Undesirable Effects

4.8.1 Clinical trial data

The safety of GYNO-DAKTARIN was evaluated in a total of 537 women with microbiologically confirmed candidiasis and symptoms (e.g., vulvovaginal itching, burning/irritation), or signs of vulvar erythema, edema, excoriation, or vaginal erythema or edema who participated in 2 single-blind clinical trials. Subjects were treated with miconazole intravaginally, randomly assigned to either a single 1,200 mg capsule, or a 7-day application of 2% vaginal cream.

Adverse Drug Reactions (ADRs) reported by ≥1% of GYNO-DAKTARIN-treated subjects in these trials are shown in Table 1

Table 1. Adverse Drug Reactions Reported by ≥1% of GYNO-DAKTARIN-treated Subjects in 2 Single Blind Clinical Trials

System/Organ Class Preferred Term	Miconazole 1,200 mg Capsule (n=272) %	Miconazole 2% Vaginal Cream 7 Days (n=265)%
Reproductive System and Breast Disorders		
Genital pruritus female	16.5	23
Vaginal burning sensation	22.8	22.6
Vulvovaginal discomfort	16.2	14.3
Dysmenorrhoea	3.3	3.4
Vaginal discharge	3.7	0.4
Vaginal haemorrhage	1.1	0.4
Vaginal pain	1.5	0.4
Nervous System Disorders		
Headache	9.6	13.6
Infections and Infestations		
Urinary tract infection	1.1	0.4
Gastrointestinal Disorders		
Abdominal pain	1.8	2.3
Abdominal pain upper	1.5	1.1
Nausea	1.5	1.1
Abdominal pain lower	1.5	0
Skin and subcutaneous Tissue Disorders		
Rash	1.1	0.4
Renal and Urinary Disorders		
Dysuria	1.1	0.4

Additional ADRs that occurred in <1% of GYNO-DAKTARIN-treated subjects (n = 537 women) in the single-blind clinical studies are listed in Table 2.

Table 2. Adverse Drug Reactions Reported by <1% of GYNO-DAKTARIN-treated Subjects in 2 Single Blind Clinical Trials

System/Organ Class Preferred Term	Miconazole 1,200 mg Capsule (n=272) %	Miconazole 2% Vaginal Cream 7 Days (n=265) %
Skin and subcutaneous tissue disorders		
Rash pruritic	0	0.4
Rosacea	0.4	0
Swelling face	0.7	0
Urticaria	0.4	0

The majority of ADRs reported in clinical trials were mild to moderate in severity.

4.8.1. Postmarketing Data

Adverse drug reactions first identified during postmarketing experience with GYNO-DAKTARIN 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

Table 3. **Adverse Drug Reactions Identified During Postmarketing Experience with GYNO-DAKTARIN by Frequency Category Estimated from Spontaneous Reporting Rates**

Immune System Disorders	
Very Rare	Hypersensitivity including Anaphylactic and Anaphylactoid reactions, Angioedema
Skin and Subcutaneous Tissue Disorders	
Very Rare	Pruritis
Reproductive System and Breast Disorders	
Very rare	Vaginal irritation
General Disorders and Administrative Site Conditions	
Very Rare	Application site reaction

4.9. Overdose

GYNO-DAKTARIN products are intended for local application and not for oral use. In the event of accidental ingestion of large quantities of GYNO-DAKTARIN products, an appropriate method of gastric emptying may be used, if considered necessary. See also Section 4.5, Interactions with other medicinal products and other forms of interaction.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

Pharmacotherapeutic classification: (Antiinfectives and antiseptics, excl. combinations with corticosteroids, imidazole derivative)
ATC code: G01A F04

Miconazole combines a potent antifungal activity against common dermatophytes and yeasts with an antibacterial activity against certain gram-positive bacilli and cocci.

Miconazole inhibits the biosynthesis of ergosterol in fungi and changes the composition of other lipid components in the membrane, resulting in fungal cell necrosis.

In general, miconazole exerts a very rapid effect on pruritus, a symptom that frequently accompanies dermatophyte and yeast infections.

5.2. Pharmacokinetic Properties

Absorption:. Miconazole persists in the vagina for up to 72 hours after a single dose. Systemic absorption of miconazole after intravaginal administration is limited, with a bioavailability of 1 to 2% following intravaginal administration of a 1200 mg dose. Plasma concentrations of miconazole are measurable within 2 hours of administration in some subjects, with maximal levels seen 12 to 24 hours after administration. Plasma concentrations decline slowly thereafter and were still measurable in most subjects 96 hours post-dose. A second dose administered 48 hours later resulted in a plasma profile similar to that of the first dose.

Distribution: Absorbed miconazole is bound to plasma proteins (88.2%) and red blood cells (10.6%).

Metabolism and Excretion: The small amount of miconazole that is absorbed is eliminated predominantly in feces as both unchanged drug and metabolites over a four-day post-administration period. Smaller amounts of unchanged drug and metabolites also appear in urine. The apparent elimination half-life ranges from 20 to 45 hours in most subjects and likely reflects both absorption from the site of application and metabolism/excretion of the drug.

5.3. Preclinical Safety Data

Preclinical data reveal no special hazard for humans based on conventional studies of local irritation, single and repeated dose toxicity, genotoxicity, and toxicity to reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

The cream formulation consists of PEG-6 (and) PEG-32 (and) glycol stearate, oleoyl macrogolglycerides, liquid paraffin, benzoic acid, butylated hydroxyanisole and purified water.

6.2. Incompatibilities

None known.

6.3. Special Precautions for Storage

Store at 25°C or below
Keep out of reach of children.

6.4. Nature and Contents of Container

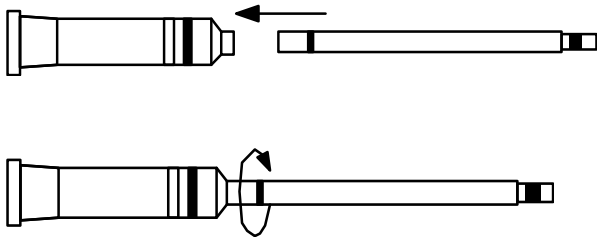
Gyno Daktarin cream is supplied in tubes containing 40g and with 7 disposable applicators..

6.5. Instructions for Use and Handling

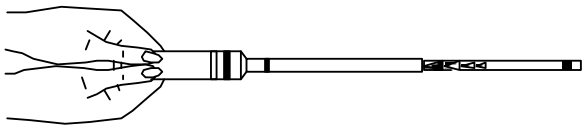
GYNO-DAKTARIN Cream

1. To open the tube unscrew the cap. Then pierce the seal of the tube using the pin on the top of the cap.

Replace the cap with the applicator.



2. Press on the end of tube to expel the cream into the applicator. If the piston shows resistance, pull gently. Fill the applicator completely unless the prescribing physician instructs otherwise.



3. Remove the applicator from the tube. Replace the cap on the tube instantly with care.

4. While lying down, knees bent and spread out, insert applicator into vagina as deeply as possible. Press piston completely to expel the cream. Remove the applicator and throw it away.

Manufacturer: Janssen Pharmaceutica, Beerse, Belgium

Registration Holder: J-C Health care ltd., Kibbutz Shefayim 60990