PRODUCT NAME
DAKTACORT™ cream

DOSAGE FORMS AND STRENGTHS
Each gram contains 20 mg miconazole nitrate and 10 mg hydrocortisone.
White, homogenous, odourless cream for topical application to the skin.
For excipients, see *List of Excipients*.

CLINICAL INFORMATION
Indications
Infections of the skin by dermatophytes or Candida spp., in which inflammatory symptoms are prominent.

Thus DAKTACORT is particularly indicated for the initial stages of treatment. Once the inflammatory symptoms have disappeared, treatment may be continued with miconazole nitrate 20 mg/g topical cream, if preferred. In view of DAKTACORT's antibacterial effect on gram-positive bacteria, the product may also be used for mycotic infections with bacterial superinfection.

Dosage and Administration
DAKTACORT™ cream should be applied topically to the lesion once to twice daily. DAKTACORT™ cream should be rubbed in gently until it has been completely penetrated into the skin. This dosage applies to both adults and children. The treatment of DAKTACORT™ cream (or subsequently miconazole nitrate 20 mg/g topical cream) should be continued without interruption until the lesion has completely disappeared (usually after 2 to 5 weeks).

Special populations
Use in infants
In infants, long term continuous topical corticosteroid therapy should be avoided (see *Warnings and Precautions*).

Use in elderly
Natural thinning of the skin occurs in the elderly; hence corticosteroids should be used sparingly and for short periods of time.

If after 7 days of treatment no improvement has occurred, cultural isolation of the infecting organism should be followed by appropriate local or systemic antimicrobial therapy

Contraindications
Known hypersensitivity to miconazole or other imidazole derivatives, hydrocortisone or another ingredient of DAKTACORT™ cream. Tuberculous skin infections, herpes simplex, vaccinia and all forms of varicella. DAKTACORT™ is not indicated for infections caused by gram negative bacteria.

Warnings and Precautions
If a reaction suggesting sensitivity or irritation should occur, the treatment should be discontinued. DAKTACORT™ must not come into contact with the mucosa of the eyes.

As with any topical corticosteroid, caution is advised with infants and children when DAKTACORT™ is to be applied to extensive surface areas or under occlusive dressings including baby napkins (diapers). Similarly application to the face should be avoided.

In infants, long term continuous topical corticosteroid therapy should be avoided. Adrenal suppression can occur even without occlusion.

Because of its corticosteroid content, avoid long-term treatment with DAKTACORT™. Once the inflammatory symptoms have disappeared, treatment may be continued with miconazole nitrate 20 mg/g cream (see *Indications*).

DAKTACORT™ can damage certain synthetic materials. Therefore, it is recommended to wear cotton underwear if this clothing comes into contact with the affected area.

Severe hypersensitivity reactions, including anaphylaxis and angioedema, have been reported during treatment with DAKTACORT™ and with other miconazole topical formulations (see *Adverse Reactions*). If a reaction suggesting hypersensitivity or irritation should occur, the treatment should be discontinued.

Contact should be avoided between latex products such as contraceptive diaphragms or condoms and DAKTACORT™ since the constituents of DAKTACORT™ may damage the latex.

Visual disturbance

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Interactions

Miconazole administered systemically is known to inhibit CYP3A4/2C9. Due to the limited systemic availability after topical application (see *Pharmacokinetic Properties*), 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 some other drugs (e.g., certain oral hypoglycemics and phenytoin), when co-administered with miconazole, can be increased and caution should be exercised.

Miconazole is a CYP3A4 inhibitor that can decrease the rate of metabolism of hydrocortisone. Serum concentrations of hydrocortisone may be higher with the use of DAKTACORT™ compared with topical preparations containing hydrocortisone alone.

Pregnancy and Breast-feeding

Pregnancy

Caution is recommended during pregnancy and lactation. Treatment of large surfaces and the application under occlusive dressing should be avoided during that time.

Miconazole has not been observed to be teratogenic in animals but has been shown to be embryotoxic at maternal toxic doses. In animals, corticosteroids are known to cross the placenta and consequently can affect the fetus (see *Non-Clinical Information*).

Breast-feeding

There are no adequate and well-controlled studies on the topical administration of DAKTACORT during breast-feeding. It is not known whether topical administration of DAKTACORT to the skin could result in sufficient systemic absorption to produce detectable quantities of hydrocortisone and miconazole in breast milk in humans. Caution is recommended during breast-feeding. Treatment of large surfaces and the application under occlusive dressing should be avoided during that time.

Adverse Reactions

Throughout this section adverse reactions are reported. Adverse reactions are adverse events that were considered to be reasonably associated with the use of miconazole nitrate and hydrocortisone based on the comprehensive assessment of the available adverse event information. A causal relationship with miconazole nitrate and hydrocortisone 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 DAKTACORT™ Cream was evaluated in 480 patients who participated in 13 clinical trials (six double-blind and seven open-label trials) of DAKTACORT™ Cream. These studies examined patients from 1 month to 95 years of age with infections of the skin caused by dermatophytes or *Candida* species in which inflammatory symptoms were prominent.

All Patients

No adverse reactions were reported by ≥1% of the 480 Daktacort Cream-treated patients (adult and paediatric patients combined).

The frequency categories use the following convention: very common (>1/10); common (>1/100 to <1/10); uncommon (>1/1,000 to <1/100); rare (>1/10,000 to <1/1,000); very rare (<1/10,000); and not known (cannot be estimated from the available clinical trial data).

Of the three adverse reactions identified from the 13 clinical trials of Daktacort Cream, skin irritation was reported in one clinical trial that included patients aged 17 to 84 years, skin burning sensation in two clinical trials that included patients aged 13 to 84 years, and irritability in one clinical trial of infants aged 1 to 34 months.

Paediatric Population

The safety of Daktacort Cream was evaluated in 63 paediatric patients (1 month to 14 years of age) who were treated with Daktacort Cream in 3 of the 13 clinical trials noted above. One adverse reaction term (irritability) was reported in these 3 trials. The frequency of irritability in Daktacort Cream-treated paediatric patients was common (3.2%).

All events of irritability occurred in one clinical trial of infants (aged 1 to 34 months) with napkin (diaper) dermatitis. The frequency, type, and severity of other adverse reactions in paediatric patients are expected to be similar to those in adults. Adverse reactions were reported by ≥1% of the 480 Daktacort Cream-treated patients (adult and paediatric patients combined).

Adverse Reactions in Adult and Paediatric Patients Treated With Daktacort Cream

System Organ Class	Adverse reactions	
	Frequency Category	
	Uncommon (≥1/1,000 to <1/100)	Not Known
Immune System Disorders		Anaphylactic reaction, Hypersensitivity
Skin and Subcutaneous Tissue Disorders	Skin irritation, Skin burning sensation, Urticaria, Pruritus	Angioedema, Rash, Contact dermatitis, Erythema, Skin inflammation, Skin hypopigmentation, Application site reaction
General Disorders and Administration Site Conditions	Irritability	
Eye disorders		Vision, blurred (see also *Warnings and Precautions*)

Overdose

Symptoms and signs

Prolonged and excessive use can result in skin irritation, which usually disappears after discontinuation of therapy. Topically applied, corticosteroids can be absorbed in sufficient amounts to produce systemic effects.

Pharmacological Properties

Pharmacodynamic Properties

Pharmacotherapeutic group: Imidazole and triazole derivatives, combinations, ATC code: D01AC20.

Mechanism of action

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

Miconazole has also been proven to be effective in secondarily infected mycoses.

Hydrocortisone is an anti-inflammatory steroid. Its anti-inflammatory action is due to reduction in the vascular component of the inflammatory response, suppression of migration of polymorphonuclear leukocytes, and reversal of increased capillary permeability. The vasoconstrictor action of hydrocortisone may also contribute to its anti-inflammatory activity.

Miconazole in combination with hydrocortisone acts very rapidly on pruritus, which frequently accompanies dermatophyte and yeast infections. This symptomatic improvement is seen before the first signs of healing are observed. However, treatment with hydrocortisone is symptomatic and lesions may flare up again after discontinuation of the treatment.

Pharmacodynamic effects

Microbiology

The clinical efficacy of miconazole has been demonstrated against dermatophytes and *Candida* spp.

Pharmacokinetic Properties

Absorption

Miconazole remains in the skin for up to 4 days after topical application. Systemic absorption of miconazole is limited, with a bioavailability of less than 1% following topical application of miconazole. Plasma concentrations of miconazole and/or its metabolites were measurable 24 and 48 hours after application. Systemic absorption has also been demonstrated after repeated application of miconazole to infants with napkin dermatitis (diaper dermatitis).

Approximately 3% of the dose of hydrocortisone is absorbed after application on the skin.

Distribution

Absorbed miconazole is bound to plasma proteins (88.2%) and red blood cells (10.6%). More than 90% of hydrocortisone is bound to plasma proteins.

Metabolism and elimination

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 half-life of hydrocortisone is about 100 minutes. Metabolism takes place in the liver and tissues and the metabolites are excreted with the urine, mostly as glucuronides, together with a very small fraction of unchanged hydrocortisone.

NON-CLINICAL INFORMATION

Preclinical data on the drug product (miconazole nitrate + hydrocortisone) revealed no special hazard for humans based on conventional studies of ocular irritation, dermal sensitization, single dose oral toxicity, primary dermal irritation toxicity, and 21-day repeat dose dermal toxicity. Additional preclinical data on the individual active ingredients in this drug product reveal no special hazard for humans based on conventional studies of local irritation, single and repeated dose toxicity, genotoxicity, and for miconazole toxicity to reproduction. Reproductive effects and developmental abnormalities have been reported with hydrocortisone in various animal models.

PHARMACEUTICAL INFORMATION

List of Excipients

Benzoic acid,
Butylated hydroxyanisole,
Disodium edetate,
Glycol stearate,
Liquid paraffin,
Oleoyl macrogolglycerides,
PEG-6 & PEG-32,
Purified water

Incompatibilities

Contact should be avoided between latex products such as contraceptive diaphragms or condoms and DAKTACORT™ since the constituents of DAKTACORT™ may damage the latex.

Shelf Life

See expiry date on the outer pack.

Storage Conditions
Store in a refrigerator (between 2° and 8°C).
Keep out of sight and reach of children.

Nature and Contents of Container
DAKTACORT™ cream (containing 20mg of miconazole nitrate per gram and 10mg hydrocortisone per gram) is supplied in tubes of 15g cream.

Instructions for Use and Handling
To open the tube, unscrew the cap. Then pierce the seal of the tube with the pin on the top of the cap.

BATCH RELEASER
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