

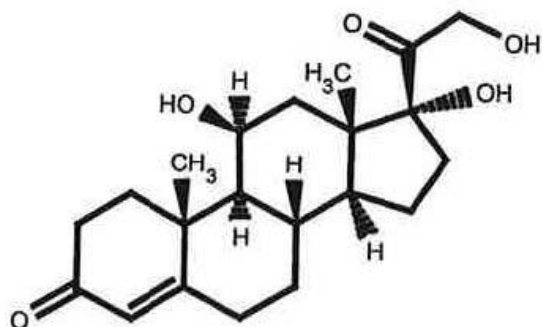
PRODUCT INFORMATION

HYDROZOLE[®] CREAM 1%

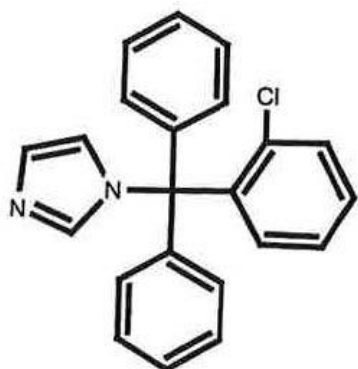
NAME OF THE MEDICINE

HYDROZOLE cream contains the active ingredients hydrocortisone and clotrimazole.

Hydrocortisone: Chemical name: 11 β , 17 α , 21-trihydroxypregn-4-ene-3, 20-dione. Molecular formula: C₂₁H₃₀O₅. MW: 362.5, CAS: 50-23-7. Hydrocortisone is an odourless, white or almost white crystalline powder. It is practically insoluble in water, sparingly soluble in acetone and in alcohol, slightly soluble in methylene chloride, very slightly soluble in ether.



Clotrimazole: Chemical name: 1-(o-chloro- α -diphenylbenzyl) imidazole. Molecular formula: C₂₂H₁₇ClN₂. MW: 344.84. CAS: 23593-75-1. Melting point: 141 to 145°C. It is a colourless, crystalline, weakly alkaline substance, soluble in acetone, chloroform and ethanol and practically insoluble in water. It forms stable salts with both organic and inorganic acids. It is not photosensitive but is slightly hygroscopic, and may be hydrolysed in acid media. The structural formula is given below:



DESCRIPTION

HYDROZOLE contains the active ingredients hydrocortisone (microfine) 1% w/w and clotrimazole 1% w/w.

HYDROZOLE also contains cetomacrogol 1000, glycerol, cetostearyl alcohol, light liquid paraffin, soft white paraffin, propylene glycol, purified water and chlorocresol 0.2% as a preservative. The cream (nonionic) is lanolin free and does not contain parabens preservatives.

Topical corticosteroid/ antifungal. On topical application, corticosteroids (hydrocortisone) produce anti-inflammatory, antipruritic and vasoconstrictor actions. The activity of the drugs is thought to result at least in part from binding with a steroid receptor.

Clotrimazole is a broad spectrum antifungal agent that is used for the treatment of dermal infections caused by various species of pathogenic dermatophytes, yeast and *Pityrosporum orbiculare*. The antifungal action appears to be on the cell membrane of the fungi, damaging the permeability barrier.

PHARMACOLOGY

Hydrocortisone. Corticosteroid, which in general, decreases inflammation by stabilising leucocyte lysosomal membranes; preventing the release of the destructive contents from leucocytes; inhibiting macrophage accumulation in inflamed areas; reducing leucocyte adhesion to the capillary endothelium; reducing capillary wall permeability and oedema formation; decreasing complement components; antagonising histamine activity and release of kinin from substrates; reducing fibroblast proliferation, collagen deposition, and subsequent scar tissue formation; and possibly by other mechanisms as yet unknown.

Clotrimazole. Synthetic imidazole derivative with broad spectrum antifungal activity and some antibacterial activity. It exerts its antifungal activity by altering cell membrane permeability by interfering with ergosterol synthesis. The cell membrane is unable to function as a selective barrier, and potassium and other cellular constituents are lost.

Clotrimazole is effective against a wide variety of fungi, including yeasts and dermatophytes. *In vitro*, clotrimazole concentrations of 1 µg/mL or less inhibit most strains of *Trichophyton rubrum*, *T. mentagrophytes*, *Epidermophyton floccosum* and *Microsporum canis*. At a concentration of 3 µg/mL or less, clotrimazole inhibits most other susceptible organisms including *Pityrosporum orbiculare*, *Aspergillus fumigatus*, *Candida albicans*, some strains of *Staphylococcus aureus* and *Streptococcus pyogenes* and a few strains of *Proteus vulgaris* and *Salmonella*.

Pharmacokinetics

Hydrocortisone. The rate and extent of hydrocortisone absorption through the skin varies among individual patients. Following topical application of a corticosteroid to most areas of normal skin, only minimal amounts of the lipophilic drug partitions into the

predominantly aqueous dermoepidermal layer (visible epidermis and dermis) and subsequently into the systemic circulation.

Absorption is, however, markedly increased when the skin has lost its keratin layer or the rate limiting properties of the stratum corneum. Physical disruption of the stratum corneum, inflammation and/or disease to the epidermal barrier (e.g. psoriasis, eczema) may result in increased absorption. Hydrocortisone is absorbed to a greater degree from the skin of the ear region (around and behind), scrotum, axilla, eyelid, face and scalp than from the skin of the forearm, knee, elbow, palm and sole. Prolonged absorption persists even after the area of application has been washed, possibly because the drug is retained in the stratum corneum and/or the dermoepidermal layer.

Hydrocortisone is metabolised by the liver and most other tissues to hydrogenated and degraded forms such as tetrahydrocortisone and tetrahydrocortisol. These are excreted in urine mainly conjugated as glucuronides, together with a very small proportion of unchanged hydrocortisone.

Children are at a greater risk of systemic absorption of topical steroids due to higher permeation properties of the skin and increased surface area to body mass ratio.

Clotrimazole. Following topical application to the skin, only very small amounts of clotrimazole appear to be absorbed systemically. Six hours after the topical application of labelled clotrimazole, the concentration of clotrimazole ranged from 100 $\mu\text{g}/\text{cm}^3$ in the stratum corneum to 0.05 to 1 $\mu\text{g}/\text{cm}^3$ in the stratum reticulare and 0.1 $\mu\text{g}/\text{cm}^3$ in the subcutis. No measurable radioactivity was found in the serum within 48 hours after application of 0.8 g of a 1% cream.

Studies of urinary excretion have shown that less than 0.5% of dermally applied clotrimazole appears in the urine over a five day period of observation. Faecal excretion, the route by which most of the absorbed drug is likely to be eliminated, has not been studied in humans.

INDICATIONS

For dermatophyte and yeast infections of the skin when inflammation is prominent. This includes conditions such as fungal infected dermatitis, intertrigo and Candida nappy rash.

CONTRAINDICATIONS

HYDROZOLE cream is contraindicated for use:

- in patients with known history of hypersensitivity to hydrocortisone, clotrimazole or any components of the formulation
- in tuberculous conditions of the skin, acute *Herpes simplex*, vaccinia, varicella

and all viral infections

- in primary infected skin lesions caused by infection with fungi or yeasts when inflammation is not prominent
- in primary or secondary infections due to bacteria
- in rosacea
- in acne vulgaris
- in pruritus without inflammation
- in the eyes
- in patients with markedly impaired circulation since skin ulceration has occurred in these patients following the use of corticosteroids
- on occluded areas of skin.

PRECAUTIONS

For external use only.

Reversible hypothalamic-pituitary-adrenal (HPA) axis suppression

Manifestations of hypercortisolism (Cushing's syndrome) and reversible hypothalamic-pituitary-adrenal (HPA) axis suppression can occur in some individuals as a result of increased systemic absorption of topical corticosteroids. There may be a need for periodic evaluation for hypothalamo-pituitary-adrenal (HPA)-axis suppression by using the urinary free cortisol test or the corticotrophin stimulation test. If either of the above are observed, withdraw the drug gradually by reducing the frequency of application, or by substituting a less potent corticosteroid. Abrupt withdrawal of treatment may result in glucocorticosteroid insufficiency (see **ADVERSE EFFECTS**).

Risk factors for increased corticosteroidal systemic effects are:

- Potency and formulation of topical steroid
- Duration of exposure
- Application to a large surface area
- Use on occluded areas of skin e.g. on intertriginous areas or under occlusive dressings (in infants the nappy may act as an occlusive dressing)
- Increasing hydration of the stratum corneum

- Use on thin skin areas such as the face
- Use on broken skin or other conditions where the skin barrier may be impaired

Infection

Extension of the infection may occur due to the masking effect of the steroid. Any spread of infection requires withdrawal of topical corticosteroid therapy and administration of appropriate antimicrobial therapy.

The immunosuppressive effects of topical corticosteroids may impair the normal function of T cells and macrophages. The result of such impairment may be the activation of latent infection or exacerbation of intercurrent infections, including those caused by *Mycobacterium*, *Toxoplasma*, *Strongyloides*, *Pneumocystis*, *Cryptococcus*, *Nocardia* and amoeba. Therefore topical corticosteroids should be used with caution in patients with impaired T cell function or in those patients receiving other immunosuppressive therapy.

Application to the face

Prolonged application to the face is undesirable as this area is more susceptible to atrophic changes.

Application to the eyelids

If applied to the eyelids, care is needed to ensure that the preparation does not enter the eye, as cataracts and glaucoma might result from repeated exposure.

Chronic leg ulcers

Topical corticosteroids are sometimes used to treat the dermatitis around chronic leg ulcers. However, this use may be associated with a higher occurrence of local hypersensitivity reactions and an increased risk of local infection.

Local hypersensitivity

Local hypersensitivity reactions may resemble symptoms of the condition under treatment (see **ADVERSE EFFECTS**). If signs of hypersensitivity appear, application should be stopped and alternative therapy instituted.

Dilution

Products which contain antimicrobial agents should not be diluted.

Contraceptives

This product may cause damage to latex contraceptives. Consequently the effectiveness of such contraceptives may be reduced. Patients should be advised to

use alternative precautions during treatment and for at least five days after cessation of treatment.

Psoriasis

Topical corticosteroids should be used with caution in the management of psoriasis, as exacerbation of the disease or pustular psoriasis may occur during or on withdrawal of topical corticosteroid therapy.

Renal / Hepatic Impairment

The minimum quantity should be used for the shortest duration to achieve the desired clinical benefit.

Use in pregnancy (Category A)

Topical administration of corticosteroids to pregnant animals can cause abnormalities of foetal development. The relevance of this finding to human beings has not been established.

Well-conducted epidemiological studies have not identified adverse events of clotrimazole on pregnancy or on the health of the foetus.

Administration of hydrocortisone with clotrimazole during pregnancy should only be considered if the expected benefit to the mother outweighs the risk to the foetus. HYDROZOLE should not be used on extensive areas in pregnant women. The minimum quantity should be used for the minimum duration.

Use in lactation

It is not known whether topical administration of hydrocortisone with clotrimazole could result in sufficient systemic absorption to produce detectable amounts in breast milk. However, systemic corticosteroids are distributed into breast milk.

Administration of HYDROZOLE during lactation should only be considered if the expected benefit to the mother outweighs the risk to the infant.

If used during lactation, HYDROZOLE should not be applied to the breasts to avoid accidental ingestion by the infant.

Paediatric use

Hydrocortisone. In comparison with adults, children and infants may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic adverse effects. This is because children have an immature skin barrier and a

osteoporosis, glaucoma, hyperglycaemia/glucosuria, cataract, hypertension, increased weight/obesity, decreased endogenous cortisol levels, steroid withdrawal syndrome

Skin and Subcutaneous Tissue Disorders

Not known: Allergic contact dermatitis/dermatitis, urticaria, skin atrophy, pigmentation changes, exacerbation of underlying symptoms, skin burning/skin pain, hypertrichosis, rash, pruritus, erythema, dry skin, skin striae, blisters, skin exfoliation, irritation, skin oedema, hyperaesthesia, skin cracking, thinning and tightening, rosacea, telangiectasia, increased fragility of cutaneous blood vessels, folliculitis, acne eruption, perioral dermatitis, maceration, miliaria, purpura.

Adverse dermatological effects usually improve when treatment is discontinued but may persist for long periods, atrophic striae may be permanent. Adverse dermatological effects are most likely to occur in intertriginous and facial areas.

DOSAGE AND ADMINISTRATION

For topical use only.

The cream should be applied on clean dry areas of affected skin.

Apply thinly and gently rub in using only enough to cover the entire affected area twice a day for up to seven days. Regular application is essential for successful treatment, whether or not a cure is confirmed mycologically.

If an emollient is being used, allow adequate time for absorption after each application before applying the emollient.

Patients should be advised to wash their hands after applying HYDROZOLE cream, unless it is the hands that are being treated.

Treatment should not be continued for more than seven days without medical supervision. If the condition worsens or does not improve within seven days, treatment and diagnosis should be re-evaluated.

To prevent relapse of fungal infection, all possibly infected areas should be treated at the same time and treatment with an appropriate topical antifungal should be continued for at least two weeks after disappearance of all signs of infection.

Rebound of pre-existing dermatoses can occur with abrupt discontinuation of topical corticosteroids. If an affected dermatitis requires further treatment to achieve control of the pre-existing dermatoses, once the fungal infection is treated, it may be necessary to continue therapy with another corticosteroid preparation not containing clotrimazole.

Note. Nonocclusive loose clothing should be worn during treatment of any affected area normally covered by clothing.

Children

Children are more likely to develop local and systemic side effects of topical corticosteroids and in general, require shorter courses of treatment than adults (see **PRECAUTIONS**).

Care should be taken when using hydrocortisone with clotrimazole to ensure the amount applied is the minimum that provides therapeutic benefit.

Elderly

The minimum quantity should be used for the shortest duration to achieve the desired clinical benefit.

Renal / Hepatic Impairment

The minimum quantity should be used for the shortest duration to achieve the desired clinical benefit.

OVERDOSAGE

Symptoms and signs

Topically applied hydrocortisone with clotrimazole may be absorbed in sufficient amounts to produce systemic effects. Acute overdosage is very unlikely to occur, however, in the case of chronic overdosage or misuse the features of hypercortisolism may occur (see **PRECAUTIONS**, **ADVERSE EFFECTS**). Dizziness, nausea and vomiting may be seen.

Treatment

In the event of chronic overdosage or misuse, topical corticosteroids should be withdrawn gradually by reducing the frequency of application because of the risk of adrenal insufficiency.

Further management should be as clinically indicated or as recommended by the Poisons Information Centre (telephone 13 11 26).

PRESENTATION AND STORAGE CONDITIONS

HYDROZOLE cream contains hydrocortisone 1% w/w and clotrimazole 1% w/w. The product is presented in tubes of 2 g and 5 g (samples), 30 g and 50 g.

Not all pack sizes may be distributed in Australia.

Store below 25°C.

NAME AND ADDRESS OF THE SPONSOR

GlaxoSmithKline Australia Pty Ltd Consumer Healthcare Division

82 Hughes Avenue
Ermington NSW 2115
AUSTRALIA

POISON SCHEDULE

Schedule 3 - Pharmacist Only Medicine (2 g, 5 g and 30 g)

Schedule 4 - Prescription Only Medicine (50 g).

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG): 2 July 2008

Date of most recent amendment: 5 November 2014

Hydrozole[®] is a registered trade mark of Stiefel Laboratories, Inc.

Version 6.0

