AUSTRALIAN PRODUCT INFORMATION – HYDROZOLE CREAM 1% (HYDROCORTISONE AND CLOTRIMAZOLE)

1 NAME OF THE MEDICINE

HYDROZOLE cream contains the active ingredients hydrocortisone and clotrimazole.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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.

3 PHARMACEUTICAL FORM

Hydrozole Cream is a smooth, non-greasy white cream.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC 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.

4.2 DOSE AND METHOD OF 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. Non occlusive loose clothing should be worn during treatment of any affected area normally covered by clothing.

Paediatric Use
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**).

4.3 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.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Identified 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

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.

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.

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 greater surface area to body weight ratio compared with adults. Care should be taken when using hydrocortisone with clotrimazole to ensure the amount applied is the minimum that provides therapeutic benefit.

In infants and children under 12 years of age, long-term continuous topical corticosteroid therapy should be avoided where possible, as adrenal suppression can occur.

HPA-axis suppression, Cushing's syndrome and intracranial hypertension have occurred in children receiving topical corticosteroid. Manifestations of adrenal suppression in children include retardation of linear growth, delayed weight gain, low plasma cortisol concentrations and lack of response to corticotrophin stimulation (see Actions, Pharmacokinetics). Manifestations of intracranial hypertension include bulging fontanelles, headache, and bilateral papilloedema. Parents should be advised not to use tight fitting nappies or plastic pants on a child being treated in the area of the nappy, since such garments may constitute occlusive dressings.

Clotrimazole. Safety and effectiveness in children have been established for clotrimazole when used as recommended for approved indications.

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

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Co-administered drugs that can inhibit CYP3A4 (e.g. ritonavir, itraconazole) have been shown to inhibit the metabolism of corticosteroids leading to increased systemic exposure. The extent to which this interaction is clinically relevant depends on the dose and route of administration of the corticosteroids and the potency of the CYP3A4 inhibitor.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no data in humans to evaluate the effect of topical hydrocortisone with clotrimazole on fertility.

Use in pregnancy – 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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration. There have been no studies to investigate the effect of hydrocortisone with clotrimazole on driving performance or the ability to operate machinery. A detrimental effect on such activities would not be anticipated from the adverse reaction profile of topical hydrocortisone with clotrimazole.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

Although adverse reactions are not ordinarily encountered with the topical application of hydrocortisone or clotrimazole, as with all drugs patients may react adversely to either one or both of these agents when applied topically as a combination.

Adverse drug reactions (ADRs) are listed below by MedDRA system organ class and by frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 and <1/10),

uncommon (≥1/1,000 and <1/100), rare (≥1/10,000 and <1/1,000) and very rare (<1/10,000), including isolated reports.

Post-marketing data
Immune System Disorders

Very rare	Hypersensitivity

Endocrine Disorders

Very rare	Hypothalamic-pituitary adrenal (HPA) axis suppression: Cushingoid features (e.g. moon face, central obesity), delayed weight gain/growth retardation in children, 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, foliculitis, acne eruption, perioral dermatitis, maceration, miliaria, purpura.

Eye disorders

Not known	Vision blurred

General Disorders and Administration Site Conditions

Very rare	Application site irritation/pain

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.

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

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).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Topical corticosteroid/ antifungal.

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.

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.

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 1µg/mL or less inhibit most strains of *Trichophyton rubrum, T. mentagrophytes, Epidermophyton floccosum and Microsporum canis.* At a concentration of 3µg/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*.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

No data are available on the absorption of hydrocortisone with clotrimazole, however, there is no indication that absorption of hydrocortisone and clotrimazole in combination differs from that of each active alone.

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. psoriases, 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.

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 µg/cm^3 in the stratum corneum to 0.05 to 1µg/ cm^3 in the stratum reticulare and 0.1 µg/ 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.

Distribution

Hydrocortisone

Once absorbed into the systemic circulation, corticosteroids are rapidly distributed to all body tissues.

Clotrimazole

Once absorbed into the systemic circulation, clotrimazole is 90% protein bound.

Metabolism

Hydrocortisone

Hydrocortisone is metabolised by the liver and most other tissues to hydrogenated and degraded forms such as tetrahydrocortisone and tetrahydrocortisol.

Clotrimazole

Clotrimazole is metabolised in the liver to inactive substances.

Excretion

Hydrocortisone

These are excreted in urine mainly conjugated as glucoronides, together with a very small proportion of unchanged hydrocortisone.

Clotrimazole

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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Hydrocortisone

Hydrocortisone was not mutagenic in a bacterial mutagenicity assay (Salmonella typhimurium) in the absence or presence of metabolic activation, and was not genotoxic in an unscheduled DNA synthesis (UDS) assay in rat primary hepatocytes. Hydrocortisone was genotoxic in a chromosome aberration assay in human lymphocytes, and a mouse bone marrow micronucleus/sister chromatid exchange assay.

Clotrimazole

Clotrimazole was not mutagenic in the fluctuation assay with Klebsiella pneumonia and Escherichia coli K12 and was not mutagenic in the plate-incorporation assay with and without metabolic activation in S. typhimurium strains TA98 and TA100. Clotrimazole was not mutagenic in an in vivo study in Chinese hamsters.

Carcinogenicity

Hydrocortisone

Hydrocortisone was not carcinogenic in rats when administered via the subcutaneous route for 52 weeks.

Clotrimazole

Clotrimazole was not carcinogenic in rats when administered orally for 18 months.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Refer to Section 2 - Qualitative and quantitative composition.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging. [optional]

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

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. [AUST R 10319].

Not all pack sizes may be distributed in Australia.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

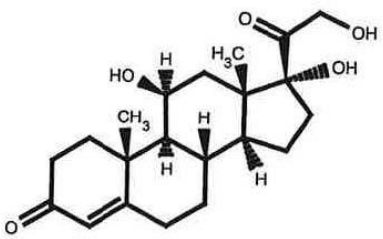
6.7 PHYSICOCHEMICAL PROPERTIES

Hydrocortisone: Chemical name: 11β, 17α, 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.

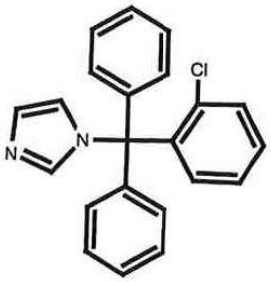
Clotrimazole: Chemical name: 1-(o-chloro-αα-diphenylbenzyl) imidazole. Molecular formula: $C_{22}H_{17}ClN_2$. MW: 344.84. CAS: 23593-75-1. Melting point: 141 to 145°C. It is a colourless, crystalline, weakly alkaline substance, soluble in acetone, chloroform and ethanol and practically insoluble in 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.

Chemical structure

Hydrocortisone



Clotrimazole



CAS number

Hydrocortisone: 50-23-7

Clotrimazole: 23593-75-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

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

Schedule 4 - Prescription Only Medicine (50 g).

8 SPONSOR

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FREECALL Australia: 1800 028 533

9 DATE OF FIRST APPROVAL

2 July 2008

10 DATE OF REVISION

17 March 2023

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Updated to the revised Australian product information format and update sponsor information.