Summary of Product Characteristics

1. Name of the medicinal product

Hydroagisten® cream

2. Qualitative and quantitative composition

Clotrimazole 1% w/w and hydrocortisone Acetate 1% w/w
Excipient with known effect: cetostearyl alcohol.
For the full list of excipients, see section 6.1

3. Pharmaceutical form

Cream.
Off white cream

4. Clinical particulars

4.1. Therapeutic indications

Skin inflammation involving fungal infection.

4.2. Posology and method of administration

Posology:
Hydroagisten cream should be thinly and evenly applied to the affected area twice daily and rubbed in gently. Treatment should be for a maximum of 7 days.
A total daily dose of 10 mg cream per kg body weight should not be exceeded. For an adult weighing 50 kg the maximum daily dose is 500 mg cream which equals approximately 2 cm of cream to be divided into 2 applications per day.
There is no separate dosage schedule for the elderly or the young. However, long-term therapy to extensive areas of skin should be avoided particularly in infants and children.

Treatment duration:
If the acute symptoms have subsided after about 7 days but treatment is still required, this may be carried out with the corticoid-free preparation intended for this purpose.

4.3. Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Use on broken skin.
- Diseases affecting the skin (e.g. acne, rosacea, perioral dermatitis, lues, tuberculosis, etc.).
- Any untreated bacterial skin diseases.
- Viral skin diseases (e.g. herpes simplex, chicken pox, shingles etc.).
- Dermal vaccination reactions.

4.4. Special warnings and precautions for use

Because of its corticosteroid content, Hydroagisten cream should not be applied:

- To large areas (more than 5 - 10% of the body surface).
- In long term continuous therapy.
- Under occlusive dressings (such as nappies and bandages).

These restrictions apply particularly in:

- Infants, where the nappy can act as an occlusive dressing and increase systemic absorption.
- Infants and children, where increased systemic absorption may occur resulting in adrenocortical suppression.
- This product contains cetostearyl alcohol, which may cause local skin reactions (e.g. contact dermatitis).

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.

4.5. Interaction with other medicinal products and other forms of interaction

Laboratory tests have suggested that, when used together, this product may cause damage to latex contraceptives. Consequently, the effectiveness of such contraceptives may be reduced. To date this has not been reflected in clinical practice.

4.6. Fertility, pregnancy and lactation

Fertility

No human studies of the effects of clotrimazole on fertility have been performed; however, animal studies have not demonstrated any effects of the drug on fertility. No data is available on the effects of topically applied hydrocortisone.

Pregnancy:

There is a limited amount of data from the use of clotrimazole or hydrocortisone in pregnant women. Animal studies with clotrimazole and corticosteroids have shown reproductive toxicity (see section 5.3). At the low systemic exposures of clotrimazole and hydrocortisone following topical treatment, harmful effects with respect to reproductive toxicity are not predicted.

Hydroagisten cream can be used during pregnancy, but only under the supervision of a physician. As a precautionary measure it is preferable to refrain from applying the cream for long periods during pregnancy.

Lactation:
Available pharmacodynamic/toxicological data in animals have shown excretion of clotrimazole/metabolites in milk after intravenous administration (see section 5.3).

No data on hydrocortisone is available, but topically applied hydrocortisone is unlikely to cause systematic effects due to the low percutaneous penetration. However, cutaneous absorption may be increased under certain circumstances, such as with use of occlusive dressing, the degree of skin damage, and the size of the treated area.

A risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue Hydrocortisone therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

4.7. Effects on ability to drive and use machines

Hydroagisten cream has no influence on the ability to drive and use machines.

4.8. Undesirable effects

As the listed undesirable effects are based on spontaneous reports, assigning accurate frequency of occurrence for each is not possible.
Immune system disorders: allergic reaction (syncope, hypotension, dyspnea, urticaria).

Skin and subcutaneous tissue disorders: blisters, discomfort/pain, oedema, erythema, irritation, peeling/exfoliation, pruritus, rash, stinging/burning.

Eye disorders: vision, blurred (see also section 4.4)

After use on large areas (more than 10% of the body surface) and/or after long-term use (longer than 2-4 weeks) or use under occlusive dressings, local skin alterations such as skin atrophy, teleangiectasias, hypertrichosis, striations, hypopigmentation, secondary infection and acneiform symptoms may occur.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health (www.Health.gov.il) according to the National Regulation by using an online form

https://sideeffects.health.gov.il

Additionally, you can also report to Padagis.co.il.

4.9. Overdose

No reports are available on cases of intoxication with Hydroagisten cream. No risk of acute intoxication is seen as it is unlikely to occur following a single dermal application of an overdose (application over a large area under conditions favorable to absorption) or inadvertent oral ingestion. There is no specific antidote

However, in the event of accidental oral ingestion, gastric lavage is rarely required and should be considered only if a life-threatening amount of Clotrimazole has been ingested within the preceding hour or if clinical symptoms of overdose become apparent (e.g. dizziness, nausea or vomiting). Gastric lavage should be carried out only if the airway can be protected adequately.

5. Pharmacological Properties

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Antifungals for topical use – imidazole and triazole derivatives, combinations.

ATC Code: D01AC20

Hydroagisten cream is a combination of clotrimazole and hydrocortisone acetate.

Mechanism of Action

Clotrimazole:

Clotrimazole acts against fungi by inhibiting ergosterol synthesis. Inhibition of ergosterol synthesis leads to structural and functional impairment of the fungal cytoplasmic membrane.

Clotrimazole has a broad antimycotic spectrum of action in vitro and in vivo, which includes dermatophytes, yeasts, moulds, etc.

Under appropriate test conditions, the MIC values for these types of fungi are in the region of less than 0.062-8.0 µg/ml substrate. The mode of action of clotrimazole is fungistatic or fungicidal depending on the concentration of clotrimazole at the site of infection. In vitro activity is limited to proliferating fungal elements; fungal spores are only slightly sensitive.

In addition to its antimycotic action, clotrimazole also acts on gram-positive microorganisms (Streptococci / Staphylococci / Gardnerella vaginalis), and gram-negative microorganisms (Bacteroides).

In vitro clotrimazole inhibits the multiplication of Corynebacteria and gram-positive cocci - with the exception of Enterococci – in concentrations of 0.5-10 µg/ml substrate.

Primary resistant variants of sensitive fungal species are very rare; the development of secondary resistance by sensitive fungi has so far only been observed in very isolated cases under therapeutic conditions.

Hydrocortisone acetate:

Hydrocortisone acetate is a weak corticosteroid with both glucocorticoid and to a lesser extent mineralocorticoid activity. As the active ingredient in a topical cream it exerts anti-phlogistic, antipruriginous, antiexudative and antiallergic effects.

Hydrocortisone acetate, like other topically applied glucocorticoids, exerts an anti-inflammatory, antiallergenic, immunosuppressive, antimitotic (antiproliferative), antipruriginous and vasoconstrictive effect on skin. Thus, in addition to the elimination of inflammation and pruritis, a normalisation of keratinisation, inhibition of excess fibroblast activity and epidermopoiesis, degradation of pathological metabolic products and inhibition of acantholysis are achieved.

However, this is not a curative therapy but rather a symptomatic treatment.

5.2. Pharmacokinetic properties

Clotrimazole:

Pharmacokinetic investigations after dermal application have shown that clotrimazole is minimally absorbed from intact or inflamed skin into the human blood circulation. The resulting peak serum concentrations of clotrimazole were below the detection limit of 0.001 µg/ml, suggesting that clotrimazole applied topically in unlikely to lead to measurable systemic effects or side effects.

Hydrocortisone acetate:

Dermal absorption of hydrocortisone acetate depends on the thickness and condition of the skin. In healthy skin no systemic effects of corticoids have been observed after local application.

However, in the case of inflamed or damaged skin, cutaneous absorption may be increased depending on the site of application, use of occlusive dressings, the degree of skin damage, and size of the treated area. Systemic effects can not be ruled out under such conditions.

An increase in the skin temperature or moisture content, e.g. in skin folds or under an occlusive dressing, also promotes absorption. In infants and small children the epidermal "barrier" is still poorly developed, which facilitates transcutaneous uptake of drugs. The occurrence of systemic effects depends partly on the dose and, to a much greater extent, on the duration of treatment.

More than 90% of the hydrocortisone acetate absorbed is bound to plasma proteins. Hydrocortisone acetate is metabolised in the liver and tissues, and the metabolites are excreted with urine. The biological half-life is approximately 100 minutes.

No relevant absorption of hydrocortisone acetate is expected after its use for a short period on limited skin inflamed areas.

5.3. Preclinical safety data

Clotrimazole:

Non-clinical data reveal no special hazard for humans based on studies of repeated dose toxicity, genotoxicity and carcinogenicity. Clotrimazole was not teratogenic in reproductive toxicity studies in mice, rats and rabbits. In rats high oral doses were associated with maternal toxicity, embryotoxicity, reduced fetal weights and decreased pup survival.

In rats clotrimazole and/or its metabolites were secreted into milk at levels higher than in plasma by a factor of 10 to 20 at 4 hrs after administration, followed by a decline to a factor of 0.4 by 24 hrs.

Hydrocortisone:

As an adrenocortical hormone, hydrocortisone is classified as relatively non-toxic for topical use. Teratogenic effects of high doses of corticosteroids including cleft palate formation, growth retardation, and fetal mortality were observed after systemic use in animal studies.

Clotrimazole plus hydrocortisone:
Non-clinical data based on acute and repeated dose toxicity studies reveal no special hazard to humans. In a 90-day repeated dose dermal study, effects were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

6. Pharmaceutical particulars

6.1. List of excipients

Purified water, 2-Octyldodecanol, Cetostearyl alcohol, Cetyl esters wax, Sorbitan monostearate, Polysorbate 60, Benzyl alcohol.

6.2. Incompatibilities

Not applicable

6.3. Shelf life

The expiry date of the product is indicated on the packaging materials.
Shelf life after first opening: 6 months.

6.4. Special precautions for storage

In a cool place, below 25°C

6.5. Nature and contents of container

Aluminium tube containing 15 g cream.
Pack sizes available: 15g

7. Marketing authorisation holder

Padagis Israel Pharmaceuticals LTD, 1 Rakefet st, Shoham

8. Registration number: 042-82-24888-00

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