SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Comagis Cream

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredients: For 100gram cream: Fluocinonide 0.05g
and Bifonazole 1.00g
Excipient with known effect: Cetostearyl Alcohol and Benzyl Alcohol.
For excipients see section 6.1.

3 PHARMACEUTICAL FORM

Cream.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Broad-spectrum drug for relief of inflammatory conditions accompanied by fungal infection, which respond to corticoid therapy.

4.2 Posology and method of administration

Adults

A small amount of the cream should be applied to the affected skin area once daily (preferably before retiring), using a gentle, but thorough massage.

Children

Administration of topical corticosteroids to pediatric patients should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of pediatric patients.

4.3 Contraindications

- Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1
- Treatment of infants with nappy rash.
- Treatment of nail and scalp infections.
- Treatment of vaginal infections.
- Application to large areas of the body or for prolonged periods must be avoided.

4.4 Special warnings and precautions for use

This product contains cetostearyl alcohol which may cause local skin reactions (e.g. contact dermatitis).
This product contains Benzyl alcohol which may cause allergic reactions and mild local irritation.

Patients with a history of hypersensitivity reactions to other imidazole antifungal agents (e.g. econazole, clotrimazole, miconazole) must take bifonazole containing products with caution.

Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients.
Conditions which augment systemic absorption include the application of the more potent steroids, use over large surface areas, prolonged use, and the addition of occlusive dressings.
Therefore, patients receiving a large dose of a potent topical steroid applied to a large surface area or under an occlusive dressing should be evaluated periodically for evidence of HPA axis suppression by using the urinary free cortisol and ACTH stimulation tests. If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid.
Recovery of HPA axis function is generally prompt and complete upon discontinuation of the drug.
Infrequently, signs and symptoms of steroid withdrawal may occur, requiring supplemental systemic corticosteroids.
Children may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity. (See Pediatric Use). If irritation develops, topical corticosteroids should be discontinued and appropriate therapy instituted.
As with any topical corticosteroid product, prolonged use may produce atrophy of the skin and subcutaneous tissues. When used on intertriginous or flexor areas, or on the face, this may occur even with short-term use.
In the presence of dermatological infections, the use of an appropriate antifungal or antibacterial agent should be instituted. If a favorable response does not occur promptly, the corticosteroid should be discontinued until the infection has been adequately controlled.

Pediatric use

Pediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced Hypothalamic-pituitary-adrenal (HPA) axis suppression and Cushing's syndrome than mature patients because of a larger skin surface area to body weight ratio.
HPA axis suppression, Cushing's syndrome, and intracranial hypertension have been reported in pediatric patients receiving topical corticosteroids. Manifestations of adrenal suppression in pediatric patients include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

4.5 Interaction with other medicinal products and other forms of interaction

Limited data suggest that an interaction between topical bifonazole and warfarin may be possible, leading to increases in INR. If bifonazole is used in a patient on warfarin therapy, they should be appropriately monitored.
Closer monitoring may be required in cases of occlusion and/or application to a large surface area or to broken and damaged skin.

4.6 Fertility, Pregnancy and lactation

Fertility

Preclinical studies gave no evidence that bifonazole can impair male or female fertility (see section 5.3).

Long-term animal studies have not been performed to evaluate the carcinogenic potential or the effect on fertility of topical corticosteroids.
Studies to determine mutagenicity with prednisolone and hydrocortisone have revealed negative results.

Pregnancy
Pregnancy category C

Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. There are no adequate and well-controlled studies in pregnant women on teratogenic effects from topically applied corticosteroids. Therefore, topical corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.

There are no clinical data from the use of bifonazole in pregnant women. Studies in animals have shown reproductive toxicity at high oral doses (see section 5.3) however these effects should not be anticipated at the low systemic exposures observed following topical bifonazole administration (see section 5.2).
Bifonazole should only be used during pregnancy after an evaluation by a doctor of the benefit to the patient and the risk to the fetus.

Lactation
It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Systemically administered corticosteroids are secreted into breast milk in quantities *not* likely to have a deleterious effect on the infant. Nevertheless, caution should be exercised when topical corticosteroids are administered to a nursing woman.

It is unknown whether bifonazole is excreted in human breast milk after topical application.
Bifonazole is excreted in milk after intravenous administration in animals (see section 5.3).
A risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue bifonazole therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.
During the lactation period bifonazole should not be applied to the chest area.

4.7 Effects on ability to drive and use machines

The medication has no or negligible influence on the ability to drive or use machinery.

4.8 Undesirable effects

• Immune system disorders
Very rarely, systemic hypersensitivity reactions may occur.

The following adverse reactions are based on spontaneous reports, thus the

frequency of individual events is not known (cannot be estimated from data).

• General disorders and administration site conditions
Administration site pain, oedema peripheral (at administration site)

• Skin and subcutaneous tissue disorders
Dermatitis contact, dermatitis allergic, erythema, pruritus, rash, urticaria, blister, skin exfoliation, eczema, dry skin, skin irritation, skin maceration, skin burning sensation

These side effects are reversible after discontinuation of the treatment.

The following local adverse reactions are reported infrequently with topical corticosteroids, but may occur more frequently with the use of occlusive dressings.

These reactions are listed in an approximate decreasing order of occurrence:
Burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, striae, miliaria.

Reporting 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 according to the National Regulation by using an online form
https://sideeffects.gov.il

In addition, you can report to Padagis via the following address:
Padagis.co.il

4.9 Overdose

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.
However, in the event of accidental oral ingestion, routine measures such as gastric lavage should be performed only 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.

Topically applied corticosteroids can be absorbed in sufficient amounts to produce systemic effects (see section 4.4).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antifungials for dermatoplogical use - Bifonazole:
ATC Code: D01A C10
Bifonazole is an imidazole derivative with a broad antimycotic spectrum, which includes dermatophytes, yeasts, moulds and other fungi such as Malassezia furfur. It is also effective against Corynebacterium minutissimum.

Bifonazole exerts its anti-fungal action by inhibiting the biosynthesis of ergosterol on two different levels. Inhibition of ergosterol synthesis leads to structural and functional impairment of the cytoplasmic membrane.

The resistance situation for bifonazole is favorable. Primary resistant variants of sensitive fungal species are very rare. Investigations so far did not provide any evidence of a development of secondary resistance in primarily sensitive strains.

Fluocinonide:
Topical corticosteroids share anti-inflammatory, anti-pruritic and vasoconstrictive actions.
The mechanism of anti-inflammatory activity of the topical corticosteroids is unclear. Various laboratory methods, including vasoconstrictor assays, are used to compare and predict potencies and/or clinical efficacies of the topical corticosteroids. There is some evidence to suggest that a recognizable correlation exists between vasoconstrictor potency and therapeutic efficacy in man.

5.2 Pharmacokinetic properties

Bifonazole absorption:
Bifonazole penetrates well into infected skin layers. 6 hours after administration concentrations in the various skin layers reach from 1000 µg/cm^3 in the top layer of the epidermis (stratum corneum) to 5 µg/cm^3 in the stratum papillare. All concentrations determined are thus within a range of reliable antimycotic activity.

After a single application (topical) of 15.2mg [^{14}C] bifonazole cream, and subsequent occlusion for six hours, 0.6±0.3% of the dose was absorbed. The absorption rate was approximately 0.008mg/100cm^2 per hour. In inflamed skin these values were higher by a factor of four. Similar results were obtained after the application of bifonazole as a 1% solution.
Plasma levels up to 16ng/ml were obtained in babies with nappy rash after a single 5g application of the cream.
After intravenous administration of 0.016mg/kg [^{14}C] bifonazole, tissue uptake was rapid. Bifonazole is, however, rapidly metabolised with only 30% of an intravenous dose remaining unaltered 30 minutes post-dose.

Bifonazole elimination:
Elimination of the metabolites is biphasic ($T_{½}$ of eight and 50 hours). Within five days of administration 45% of the administered dose has been excreted renally, with 40% being eliminated via the liver and bile (faeces).

Fluocinonide:
The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle, the integrity of the epidermal barrier, and the use of occlusive dressings.
Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin increase percutaneous absorption. Occlusive dressings substantially increase the percutaneous absorption of topical corticosteroids. Thus, occlusive dressings may be a valuable therapeutic adjunct for treatment of resistant dermatoses.
Once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systemically administered corticosteroids. Corticosteroids are bound to plasma proteins in varying degrees. Corticosteroids are metabolized primarily in the liver and are then excreted by the kidneys. Some of the topical corticosteroids and their metabolites are also excreted into the bile.

5.3 Preclinical safety data

Bifonazole:

Toxicological studies showed good local tolerability of topical formulations. With bifonazole cream slight skin irritant effects were observed which could be attributed to the excipient 2-octyldodecanol. There were no indications of changes caused specifically by the active substance, and no signs of any systemic effects were observed.

Preclinical data on oral dosage forms reveal no special hazards for humans based on conventional studies of single dose toxicity and genotoxicity. Effects on the liver (enzyme induction, fatty degeneration) were observed in repeated dose toxicity studies with oral administration but only at exposures in excess of the maximum human exposure indicating little relevance to clinical use. No carcinogenicity studies were performed with bifonazole.

In reproduction toxicology studies in rats and rabbits, oral doses of 30 mg/kg body weight resulted in embryotoxicity including lethality. In the rats, bifonazole at oral doses up to 100 mg/kg body weight was not embryotoxic, but a retarded skeletal development in the fetuses was observed at the dose of 100 mg/kg. This fetal effect on the skeletal development can be considered as a secondary effect resulting from the maternal toxicity (a reduction in body weight).

Given the low absorption of the active ingredient via the skin these results have little relevance to clinical use. In a study of lactating rats treated with radioactively labelled bifonazole (10 mg/kg body weight intravenous), approximately 3.2% of the dose was excreted in the milk. In another study of radioactively labelled bifonazole, it was found that intravenously administered bifonazole (10mg/kg body weight) passes through the placental barrier in rats.

No impairment of male or female fertility was observed in rats at oral doses up to 40 mg/kg body weight.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cetostearyl alcohol, 2-octyldodecanol, cetyl esters wax, sorbitan monostearate, polysorbate 60, benzyl alcohol, purified water.

6.2 Incompatibilities

None Known.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

Can be used for 6 months after first opening, but not later than the expiry date.

6.4 Special precautions for storage

Store below 25°C

6.5 Nature and contents of container

Aluminium tubes, in pack sizes of 7g and 15g.

Not all pack sizes may be marketed.

7 MANUFACTURER AND REGISTRATION HOLDER

Padagis Israel Pharmaceuticals Ltd.
1 RAKEFET ST.SHOHAM, 083705, ISRAEL

8 REGISTRATION NUMBER OF THE MEDICINE AT THE NATIONAL DRUG REGISTRY OF THE MINISTRY OF HEALTH

063-04-26742-00.

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