PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

PROTOPIC® 0,03 % ointment

PROTOPIC® 0,1 % ointment

COMPOSITION

1 g of PROTOPIC® 0,03 % ointment contains 0,3 mg of tacrolimus as tacrolimus monohydrate (0,03 %).

1 g of PROTOPIC® 0,1 % ointment contains 1,0 mg of tacrolimus as tacrolimus monohydrate (0,1 %).

Excipients: Hard paraffin, liquid paraffin, propylene carbonate, white beeswax, white soft paraffin.

Exposure of the skin to sunlight should be minimised and the use of ultraviolet (UV) light from a solarium, therapy with UVB or UVA in combination with psoralens (PUVA) should be avoided during the use of PROTOPIC® ointment. Medical professionals should advise patients on appropriate sun protection methods, such as minimisation of the time in the sun, use of a sunscreen product and covering of the skin with appropriate clothing.

CATEGORY ANO CLASS

A13.12 Other Dermatological Preparations

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

The mechanism of action of tacrolimus in atopic dermatitis is not fully understood. Via its binding to a specific cytoplasmic immunophilin (FKBP12), tacrolimus inhibits calcium-dependent signal transduction pathways in T cells, thereby preventing the transcription and synthesis of IL-2, IL-3, IL-4, IL-5 and other cytokines such as GM-CSF, TNF-a. and IFN-y.

In vitro, in Langerhans cells isolated from normal human skin, tacrolimus reduced the stimulatory activity towards T cells. Tacrolimus has also been shown to inhibit the release of inflammatory mediators from skin mast cells, basophifs and eosinophils.
In patients with atopic dermatitis, improvement of skin lesions during treatment with tacrolimus ointment was associated with reduced Fe receptor expression on Langerhans cells and a reduction of their hyperstimulatory activity towards T cells. Tacrolimus ointment does not affect collagen synthesis in humans.

Pharmacokinetic properties

Clinical data have shown that tacrofimus concentrations in systemic circulation after topical administration are low and, when measurable, transient.

Absorption

Data from healthy human subjects indicate that there is little or no systemic exposure to tacrolimus following single or repeated topical application of tacrolimus ointment.
Most atopic dermatitis patients (adults and children) treated with single or repeated application of tacrolimus ointment (0,03-0,1 %) had blood concentrations <1.0 ng/ml. When observed, blood concentrations exceeding 1,0 ng/ml were transient. Systemic exposure increases with increasing treatment areas. In both adults and children with an average of 50 % body surface area treated, systemic exposure (i.e. AUC) of tacrolimus from Protopic is approximately 30-fold less than seen with oral immunosuppressive doses in kidney and liver transplant patients. The lowest tacrolimus blood concentration at which systemic effects can be observed is not known.

There was no evidence of systemic accumulation of tacrolimus in patients (adults and children) treated for prolonged periods (up to one year) with tacrolimus ointment.

Distribution

Following topical application of tacrolimus ointment, tacrolimus is selectively delivered to the skin with minimal diffusion into the systemic circulation. The high binding of tacrolimus (> 98,8 %) to plasma proteins is considered not to be clinically relevant.

Metabolism

Metabolism of tacrolimus by human skin was not detectable. Systemically available tacrolimus is extensively metabolised in the liver via CYP3A4.

Elimination

When administered intravenously, tacrolimus has been shown to have a low clearance rate. The average total body clearance is approximately 2,25 1/h. The hepatic clearance of systemically available tacrolimus could be reduced in subjects with severe hepatic impairment, or in subjects who are co-treated with drugs that are potent inhibitors of CYP3A4.

Following repeated topical application of the ointment the average half-life of tacrolimus was estimated to be 75 hours for adults and 65 hours for children.

Paediatric population

The pharmacokinetics of tacrolimus after topical application are similar to those reported in adults.

INDICATIONS

Flare treatment

Adults and adolescents (16 years of age and above)

Treatment of moderate to severe atopic dermatitis in adults who are not adequately responsive to or are intolerant of topical corticosteroids.

Children (2 years of age and above)

Treatment of moderate to severe atopic dermatitis in children who failed to respond adequately to topical corticosteroids.

Maintenance treatment

Treatment of moderate to severe atopic dermatitis for the prevention of flares and the prolongation of flare-free intervals in patients experiencing a high frequency of disease exacerbations (i.e. occurring 4 or more times per year) who have had an initial response to a maximum of 6 weeks treatment of twice daily tacrolimus ointment (lesions cleared, almost cleared or mildly affected).

CONTRAINDICATIONS

- Hypersensitivity to macrolides in general, to tacrolimus or to any of the excipients (see COMPOSITION).
- Immunocompromised adults and children.
- Pregnancy and lactation (see HUMAN REPRODUCTION).
- When live attenuated vaccine(s) are used {see INTERACTIONS: Paediatric population)

WARNINGS AND SPECIAL PRECAUTIONS

PROTOPIC® should not be used in patients with congenital or acquired immunodeficiencies or in patients on therapy that cause immunosuppression. The effect of treatment with PROTOPIC® ointment on the developing immune system of children aged below 2 years has not been established.

Exposure of the skin to sunlight should be minimised and the use of ultraviolet (UV) light from a solarium, therapy with UVB or UVA in combination with psoralens (PUVA) should be avoided during use of PROTOPIC® ointment. Medical practitioners should advise patients on appropriate sun protection methods, such as minimisation of the time in the sun, use of a sunscreen product and covering of the skin with appropriate clothing. PROTOPIC® ointment should not be applied to lesions that are considered to be potentially malignant or pre-malignant.

Emollients should not be applied to the same area within 2 hours of applying PROTOPIC® ointment. Concomitant use of other topical preparations has not been assessed. There is no experience with concomitant use of systemic steroids or immunosuppressive medicines. PROTOPIC® ointment has not been evaluated for its efficacy and safety in the treatment of clinically infected atopic dermatitis. Before commencing treatment with PROTOPIC® ointment, clinical infections at treatment sites should be cleared. Patients with atopic dermatitis are predisposed to superficial skin infections. Treatment with PROTOPIC® may be associated with an increased risk of folliculitis and herpes viral infections (herpes simplex dermatitis [eczema herpeticum], herpes simplex [cold sores], Kaposi's varicelliform eruption). In the presence of these infections, PROTOPIC® should not be used.

Beyond 1 year of treatment, the potential for local immunosuppression (possibly resulting in infections or cutaneous malignancies) is unknown.

PROTOPIC® contains tacrolimus which is a calcineurin inhibitor. In transplant patients prolonged systemic exposure to intense immunosuppression following systemic administration of tacrolimus, a member of the class calcineurin inhibitors, has been associated with an increased risk developing lymphomas and skin malignancies. In patients using PROTOPIC®, cases of malignancies, including cutaneous and other types of lymphoma, and skin cancers have been reported.

Lymphadenopathy was uncommonly (0,8 %) reported in clinical trials. The majority of these cases related to infections (skin, respiratory tract, tooth) and resolved with appropriate antibiotic therapy. Transplant patients receiving immunosuppressive regimens (e.g. systemic tacrolimus) are at increased risk of developing lymphoma; therefore patients who receive PROTOPIC® and develop lymphadenopathy should be monitored to ensure that the lymphadenopathy resolves. In case of persistent lymphadenopathy, the aetiology of the lymphadenopathy should be investigated. In the absence of a clear aetiology for the lymphadenopathy or in the presence of acute infectious mononucleosis, discontinuation of PROTOPIC® should be considered.

Care should be taken to avoid contact with eyes and mucous membranes. If accidentally applied to these areas, the ointment should be thoroughly wiped off and/or rinsed off with water.

The use of PROTOPIC® ointment under occlusion has not been studied in patients. Occlusive dressings are not recommended.

Patients should wash their hands after application if the hands are not intended for treatment. Tacrolimus is extensively metabolised in the liver and although blood concentrations are low following topical therapy, the ointment should be used with caution in patients with hepatic failure. The use of tacrolimus ointment is not recommended in patients with a skin barrier defect, such as Netherton's syndrome, lamellar ichthyosis, generalised erythroderma or cutaneous Graft Versus Host disease. These skin conditions may increase systemic absorption of tacrolimus. Oral use of tacrolimus is also not recommended to treat these skin conditions. Post-marketing cases of increased tacrolimus blood level have been reported in these conditions.

Care should be exercised if applying PROTOPIC® to patients with extensive skin involvement over an extended period of time, especially in children.

The development of any new change different from previous eczema within a treated area should be reviewed by the medical practitioner.

Effects on ability to drive and use machines

PROTOPIC® ointment is administered topically and is unlikely to have an effect on the ability to drive or use machines.

INTERACTIONS

Formal topical drug interaction studies with tacrolimus ointment have not been conducted. Tacrolimus is not metabolised in human skin, indicating that there is no potential for percutaneous interactions that could affect the metabolism of tacrolimus. Systemically available tacrolimus is metabolised via the hepatic Cytochrome P450 3A4 (CYP3A4). Systemic exposure from topical application of tacrolimus ointment is low (<1,0 ng/ml) and is unlikely to be affected by concomitant use of substances known to be inhibitors of CYP3A4. However, the possibility of interactions cannot be ruled out and the concomitant systemic administration of known CYP3A4 inhibitors (e.g. erythromycin, itraconazole, ketoconazole and diltiazem) in patients with widespread and/or erythrodermic disease should be done with caution.

Paediatric population

An interaction study with protein-conjugated vaccine has been investigated in children aged 2-11 years. No effect on immediate response to vaccination, the generation of immune memory, or humoral and cell-mediated immunity has been observed.

In the case of live attenuated vaccines, vaccination should be administered prior to commencement of treatment or during a treatment free interval with a period of 28 days between the last application of PROTOPIC® and the vaccination.

HUMAN REPRODUCTION

Pregnancy

Studies in animals have shown reproductive toxicity.

PROTOPIC® ointment is therefore contraindicated during pregnancy (see CONTRAINDICATIONS).

Lactation

Tacrolimus is excreted into breast milk.

Women using PROTOPIC® ointment should not breastfeed their infants (see CONTRAINDICATIONS).

DOSAGE AND DIRECTIONS FOR USE

PROTOPIC® treatment should be prescribed only by medical professionals with experience in the treatment of atopic dermatitis.

Method of administration

PROTOPIC® ointment should be applied as a thin layer to affected or commonly affected areas of the skin. PROTOPIC® ointment may be used on any part of the body, including face, neck and flexure areas, except on mucous membranes. PROTOPIC® ointment should not be applied under occlusion.

PROTOPIC® treatment should begin at the first appearance of signs and symptoms. Each affected region of the skin should be treated **with** PROTOPIC® until lesions are cleared, almost cleared or mildly affected.

Thereafter, patients are considered suitable for maintenance treatment (see below). At the first signs of recurrence (flares) of the disease symptoms, treatment should be re-initiated.

Use in adults (16 years of age and above)

Treatment should be started with PROTOPIC® 0,1 % twice a day and treatment should be continued until clearance of the lesion up to 12 months use. If symptoms recur, twice daily treatment with PROTOPIC® 0,1% should be restarted. An attempt should be made to reduce the frequency of application or to use the lower strength PROTOPIC® 0,03 % ointment if the clinical condition allows.

Generally, improvement is seen within one week of starting treatment. If no signs of improvement are seen after two weeks of treatment, further treatment options should be considered.

Elderly patients

Specific studies have not been conducted in elderly patients. However, the clinical experience available in this patient population has not shown the necessity for any dosage adjustment.

Paediatric population

Children (2 years of age and above) should use the lower strength PROTOPIC® 0,03 % ointment.

Treatment with PROTOPIC® 0,03 % should be started twice a day for up to three weeks.

Thereafter, the frequency of application should be reduced to once a day until clearance of the lesion.

PROTOPIC® is not recommended for the use in children below the age of 2 years.

Maintenance treatment:

Patients who are responding to up to 6 weeks treatment using tacrolimus ointment twice daily (lesions cleared, almost cleared or mildly affected) are suitable for maintenance treatment.

Adults and adolescents (16 years of age and above)

Adult patients should use PROTOPIC® 0,1 % ointment.

PROTOPIC® ointment should be applied once a day twice weekly (e.g. Monday and Thursday) to areas commonly affected by atopic dermatitis to prevent progression to flares. Between applications there should be 2-3 days without PROTOPIC® treatment.
After 12 months, a review of the patient's condition should be conducted by the medical practitioner and a decision taken whether to continue maintenance treatment in the absence of safety data for maintenance treatment beyond 12 months.
If signs of a flare reoccur, twice daily treatment should be re-initiated (see treatment section above).

Elderly patients

Specific studies have not been conducted in elderly patients.

Paediatric population

Children {2 years of age and above) should use the lower strength PROTOPIC® 0,03 % ointment.
PROTOPIC® ointment should be applied once a day twice weekly {e.g. Monday and Thursday) to areas commonly affected by atopic dermatitis to prevent progression to flares. Between applications there should be 2-3 days without PROTOPIC® treatment.
The review of the child's condition after 12 months treatment should include suspension of treatment to assess the need to continue this regimen and to evaluate the course of the disease.
PROTOPIC® is not recommended for the use in children below the age of 2 years.

SIDE EFFECTS

Approximately 50 % of patients experienced skin irritation adverse reactions at the site of application. Burning sensation and pruritus were very common. Erythema was a common skin irritation adverse reaction. Sensation of warmth, pain, paraesthesia and rash at the site of application were also commonly observed. Alcohol intolerance (facial flushing or skin irritation after consumption of an alcoholic beverage) was common.

Patients are at an increased risk of folliculitis, acne and herpes viral infections, such as herpes simplex, eczema herpeticum and herpes zoster.

Adverse reactions with suspected relationship to treatment are listed below by system organ class. Frequencies are defined as very common(> 1/10), common(> 1/100, < 1/10) and Uncommon(> 1/1000,< 1/100).

System Organ Class	**Very Common > 1/10**	**Common > 1/100, < 1/10**
Infections and infestations		Local skin infection regardless of specific aetiology including but not limited to: eczema herpeticum, folliculitis, herpes simplex, herpes virus infection, Kaposi's varicelliform eruption
Metabolism and nutrition disorders		Alcohol intolerance (facial flushing or skin irritation after consumption of an alcoholic beverage)
Nervous system		Paraesthesias and

disorders		dysaesthesias (hyperaesthesia, burning sensation)
Skin and subcutaneous tissue disorders	Pruritus	Acne
General disorders and administration site conditions		Application site warmth, application site erythema, application site pain, application site irritation, application site paraesthesia, application site rash

Maintenance treatment:

In a study of maintenance treatment (twice daily treatment) in adults and children with moderate and severe atopic dermatitis the following adverse events were noted to occur more frequently than in the control group: application site impetigo (7,7 % in children) and application site infections (6,4 % in children and 6,3 % in adults).

Post-marketing:

Cases of malignancies, including cutaneous and other types of lymphoma, and **skin** cancers, have been reported in patients using tacrolimus ointment.

Skin and subcutaneous tissue disorders: rosacea.

General disorders and administration site conditions: Application site oedema.

Investigations: Drug level increased.

Paediatric population:

Frequency, type and severity of adverse reactions in children are similar to those reported in adults.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Overdosage following excessive topical administration or via ingestion should be treated general supportive measures as appropriate. These may include monitoring of vital signs and observation of clinical status.

IDENTIFICATION

PROTOPIC® 0,03 % ointment: A white to slightly yellow ointment.

PROTOPIC® 0,1 % ointment: A white to slightly yellowish ointment.

PRESENTATION

PROTOPIC® 0,03 % and 0,1 % ointment are filled into white linear LOPE laminate tubes, with HOPE shoulders fitted with a white polypropylene screw cap. The tubes have a laminate orifice membrane seal.

Package sizes: 10 g, 30 g and 60 g.

STORAGE INSTRUCTIONS

Store at or below 25 °C. Keep well closed.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS

PROTOPIC® 0,03 %: A40/13.12/0219

PROTOPIC® 0,1 %: A40/13.12/0231

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Adcock Ingram Limited

1 New Road, Erand Gardens

Midrand 1685

Private Bag x69, Bryanston, 2021

vMw.adcock.com

DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION

Date of first registration: 17 April 2009

Date of last revision: 28 June 2018

adcock ingram