הודעה על החמרה (מידע בטיחות) בעלון לרופא

תאריך: __October 25 2012 __

שם תכשיר באנגלית: ____PROTOPIC 0.03% Ointment __

מספר רישום: _____127 71 30667 00_____

שם בעל הרישום:

Salomon, Levin & Elstein Ltd P.O.Box 8077 Netanya 42504

השינויים בעלון מסומנים על רקע צהוב

פרטים על השינוי/ים המבוקש/ים

טקסט חדש	טקסט נוכחי	פרק בעלון
Protopic 0.03% ointment is indicated in adults, adolescents and children from the age of 2 years. 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 conventional therapies such as topical corticosteroids. *Children (2 years of age and above)* Treatment of moderate to severe atopic dermatitis in children (~~2 years of age and above~~) who failed to respond adequately to conventional therapies such as 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).	Treatment of moderate to severe atopic dermatitis in adults who are not adequately responsive to or are intolerant of conventional therapies such as topical corticosteroids. Treatment of moderate to severe atopic dermatitis in children (2 years of age and above) who failed to respond adequately to conventional therapies such as topical corticosteroids.	**Indications**
The effect of treatment with Protopic ointment on the developing immune system of children aged below 2 years, ~~especially the young~~, has not ~~yet~~ been established ~~and this should be taken into account when prescribing to this age group~~ (see section 4.1). The use of tacrolimus ointment is not recommended in patients with a skin barrier defect, such as Netherton's syndrome, lamellar ichthyosis, generalized erythroderma	The effect of treatment with Protopic ointment on the developing immune system of children, especially the young, has not yet been established and this should be taken into account when prescribing to this age group (see section 4.1). The use of Protopic ointment in patients with genetic epidermal barrier defects such as Netherton's syndrome is not recommended due to the potential for	**Warnings and Precautions**

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. ~~The use of Protopic ointment in patients with genetic epidermal barrier defects such as Netherton's syndrome is not recommended due to the potential for permanently increased systemic absorption of tacrolimus. The safety of Protopic ointment has not been established in patients with generalised erythroderma.~~	permanently increased systemic absorption of tacrolimus. The safety of Protopic ointment has not been established in patients with generalised erythroderma.	
		Contraindications
Paediatric population An interaction study with protein-conjugated vaccine against *Neisseria menigitidis* serogroup C 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 (see section 5.1).		**Pediatrics**
Fertility There are no fertility data available. *Pregnancy* There are no adequate data from the use of tacrolimus ointment in pregnant women. Studies in animals have shown reproductive toxicity following systemic administration (see section 5.3). The potential risk for humans is unknown. Protopic ointment should not be used during pregnancy unless clearly necessary. *Breastfeeding* Human data demonstrate that, after systemic administration, tacrolimus is excreted into breast milk. Although clinical data have shown that systemic exposure from application of tacrolimus ointment is low, breast-feeding during treatment with Protopic ointment is not recommended. ~~There are no adequate data from the use of tacrolimus ointment in pregnant women. Studies in animals have shown reproductive toxicity following systemic administration (see section 5.3). The potential risk for humans is unknown.~~ ~~Protopic ointment should not be used during pregnancy unless clearly necessary.~~	There are no adequate data from the use of tacrolimus ointment in pregnant women. Studies in animals have shown reproductive toxicity following systemic administration (see section 5.3). The potential risk for humans is unknown. Protopic ointment should not be used during pregnancy unless clearly necessary. Human data demonstrate that, after systemic administration, tacrolimus is excreted into breast milk. Although clinical data have shown that systemic exposure from application of tacrolimus ointment is low, breast-feeding during treatment with Protopic ointment is not recommended.	**Fertility, Pregnancy and Lactation**

~~Human data demonstrate that, after systemic administration, tacrolimus is excreted into breast milk. Although clinical data have shown that systemic exposure from application of tacrolimus ointment is low, breast feeding during treatment with Protopic ointment is not recommended.~~

System Organ Class	Very Common ≥1/10	Common ≥1/100, <1/10	Uncommon ≥1/1000, <1/100	Not known (cannot be estimated from the available data)
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		Alcohol		

General disorders and administration site conditions

Very common: Application site burning, application site pruritus

Common: Application site warmth, application site erythema, application site pain, application site irritation, application site paraesthesia, application site rash

Infections and infestations

Common: Herpes viral infections (herpes simplex dermatitis [eczema herpeticum], herpes simplex [cold sores], Kaposi's varicelliform eruption)

Skin and subcutaneous tissue disorders

Common: Folliculitis, pruritus

Uncommon: Acne

Nervous system disorders

Common: Paraesthesias and dysaesthesias (hyperaesthesia, burning sensation)

Metabolism and nutrition disorders

Common: Alcohol intolerance (facial flushing or skin irritation after consumption of an alcoholic beverage)

The following adverse reactions have been reported during post-marketing experience:

Adverse events

and nutrition disorders		intolerance (facial flushing or skin irritation after consumption of an alcoholic beverage)			Skin and subcutaneous tissue disorders: Rosacea.	
Nervous system disorders		Paraesthesias and dysaesthesias (hyperaesthesia, burning sensation)				
Skin and subcutaneous tissue disorders		Pruritus	Acne*	Rosacea*		
General disorders and administration site conditions	Application site burning, Application site pruritus	Application site warmth, Application site erythema, Application site pain, Application site		Application site oedema*		

		irritation, Application site paraesthesia, Application site rash		
Investigations				Drug level increased* (see section 4.4)

* The adverse reaction has been reported during post-marketing experience

~~General disorders and administration site conditions~~
~~Very common: Application site burning, application site pruritus~~
~~Common: Application site warmth, application site erythema, application site pain, application site irritation, application site paraesthesia, application site rash~~

~~Infections and infestations~~
~~Common: Herpes viral infections (herpes simplex dermatitis [eczema herpeticum], herpes simplex [cold sores], Kaposi's varicelliform eruption)~~

~~Skin and subcutaneous tissue disorders~~
~~Common: Folliculitis, pruritus~~
~~Uncommon: Acne~~

~~Nervous system disorders~~
~~Common: Paraesthesias and dysaesthesias (hyperaesthesia, burning sensation)~~
~~Metabolism and nutrition disorders~~
~~Common: Alcohol intolerance (facial flushing or skin irritation after consumption of an alcoholic beverage)~~
~~The following adverse reactions have been reported during post-~~

~~marketing experience:~~ ~~Skin and subcutaneous tissue disorders:~~ ~~Rosacea.~~ *Paediatric population* Frequency, type and severity of adverse reactions in children are similar to those reported in adults.		
~~A potential interaction between vaccination and application of Protopic ointment has not been investigated. Because of the potential risk of vaccination failure, vaccination should be administered prior to commencement of treatment, or during a treatment-free interval with a period of 14 days between the last application of Protopic and the vaccination. In case of live attenuated vaccination, this period should be extended to 28 days or the use of alternative vaccines should be considered.~~	A potential interaction between vaccination and application of Protopic ointment has not been investigated. Because of the potential risk of vaccination failure, vaccination should be administered prior to commencement of treatment, or during a treatment-free interval with a period of 14 days between the last application of Protopic and the vaccination. In case of live attenuated vaccination, this period should be extended to 28 days or the use of alternative vaccines should be considered.	**Drug Interactions**
Protopic ointment is administered topically and is unlikely to have an effect on the ability to drive or use machines. ~~No studies on the effects on the ability to drive and use machines have been performed. Protopic ointment is administered topically and is unlikely to have an effect on the ability to drive or use machines.~~	No studies on the effects on the ability to drive and use machines have been performed. Protopic ointment is administered topically and is unlikely to have an effect on the ability to drive or use machines.	**Effects on ability to drive and use machines**
Protopic treatment should be initiated by physicians with experience in the diagnosis and treatment of atopic dermatitis. ~~Protopic can be used for short-term and intermittent long-term treatment. Treatment should not be continuous~~ Protopic is available in two strengths, Protopic 0.03% and Protopic 0.1% ointment. *Posology* Flare treatment Protopic can be used for short-term and intermittent long-term treatment. Treatment should not be continuous on a long-term basis. 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. *Adults and adolescents (16 years of age and above)*	Protopic should be initiated by physicians with experience in the diagnosis and treatment of atopic dermatitis. Protopic can be used for short-term and intermittent long-term treatment. Treatment should not be continuous 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. 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 (see section 4.4). Protopic is not recommended for use in children below the age of 2 years until further data are available. 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.	**Dosage and Administration**

Treatment should be started with Protopic 0.1% twice a day and treatment should be continued until clearance of the lesion. 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 should be started twice a day for up to three weeks. Afterwards the frequency of application should be reduced to once a day until clearance of the lesion (see section 4.4). Protopic ointment should not be used in children aged below 2 years until further data are available. 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 treatment, a review of the patient`s condition should be conducted by the physician and a decision taken whether to continue maintenance treatment in the absence of safety data for maintenance treatment beyond 12 months.	Treatment 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. At the first signs of recurrence (flares) of the disease symptoms, treatment should be re-initiated. Use in children (2 years of age and above) Treatment should be started twice a day for up to three weeks. Afterwards the frequency of application should be reduced to once a day until clearance of the lesion (see section 4.4). Use in adults (16 years of age and above) Protopic is available in two strengths, Protopic 0.03% and Protopic 0.1% ointment. Treatment should be started with Protopic 0.1% twice a day and treatment should be continued until clearance of the lesion. 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.	

If signs of a flare reoccur, twice daily treatment should be re-initiated (see flare treatment section above). *Elderly patients* Specific studies have not been conducted in elderly patients (see flare treatment section above). *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 ointment should not be used in children aged below 2 years until further data are available. *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 because this method of administration has not been studied in patients (see section 4.4). ~~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 (see section 4.4).~~ ~~Protopic is not recommended for use in children below the age of 2 years until further data are available.~~ ~~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.~~ ~~Treatment~~ ~~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. At the first signs of recurrence (flares) of the disease symptoms, treatment should be re-initiated.~~ ~~Use in children (2 years of age and above)~~ ~~Treatment should be started twice a day for up to three weeks. Afterwards the frequency of application should be reduced to once a day until clearance of the lesion (see section 4.4).~~ ~~Use in adults (16 years of age and above)~~ ~~Protopic is available in two strengths, Protopic 0.03% and Protopic 0.1% ointment. Treatment should be started with Protopic 0.1% twice a day and treatment should be continued until clearance of the lesion. 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.~~		
A seven-month, double blind, randomised parallel group study of paediatric patients (2-11 years) with moderate to severe atopic dermatitis was performed. In one arm patients received Protopic 0.03% ointment (n=121) twice a day for 3 weeks and thereafter once a day until clearance. In the comparator arm patients received 1% hydrocortisone acetate ointment (HA) for head and neck and 0.1% hydrocortisone butyrate ointment for trunk and limbs (n=111) twice a day for 2 weeks and subsequently HA twice a day to all affected areas. During this period all patients and control subjects (n=44) received a primary immunisation and a rechallenge with a protein-conjugate vaccine against *Neisseria menigitidis* serogroup C. The primary endpoint of this study was the response rate to vaccination, defined as the percentage of patients with a serum bactericidal antibody (SBA) titre ≥ 8 at the week 5 visit. Analysis of the response rate at week 5 showed equivalence between the treatment groups (hydrocortisone 98.3%, tacrolimus ointment 95.4%; 7-11 years: 100% in both arms). The results in the control group were similar. The primary response to vaccination was not affected.		**Pharmacodynamics**
Paediatric population The pharmacokinetics of tacrolimus after topical application are similar to those reported in adults, with minimal systemic		**Pharmacokinetics**

exposure and no evidence of accumulation (see above).		
		Instructions for use and handling and disposal