ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Protopic 0.03% ointment

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 g of Protopic 0.03% ointment contains 0.3 mg of tacrolimus as tacrolimus monohydrate (0.03%).

Excipient with known effect
Butylhydroxytoluene (E321) 15 micrograms/g ointment.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Ointment

A white to slightly yellowish ointment.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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 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).

4.2 Posology and method of administration

Protopic treatment should be initiated by physicians with experience in the diagnosis and treatment of atopic dermatitis.

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)
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
Specific studies have not been conducted in older people. 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.

If signs of a flare reoccur, twice daily treatment should be re-initiated (see flare treatment section above).

Elderly
Specific studies have not been conducted in older people (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).

4.3 Contraindications

Hypersensitivity to the active substance, macrolides in general, or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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 (see section 5.3).-Physicians 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. The development of any new change different from previous eczema within a treated area should be reviewed by the physician.

The use of tacrolimus ointment is not recommended in patients with a skin barrier defect, such as Netherton's syndrome, lamellar ichthyosis, generalized erythroderma, pyoderma gangrenosum or cutaneous Graft Versus Host Disease. These skin conditions may increase systemic absorption of tacrolimus. Post-marketing cases of increased tacrolimus blood level have been reported in these conditions. Protopic should not be used in patients with congenital or acquired immunodeficiencies or in patients on therapy that cause immunosuppression.

Care should be exercised if applying Protopic to patients with extensive skin involvement over an extended period of time, especially in children (see section 4.2). Patients, particularly paediatric patients should be continuously evaluated during treatment with Protopic with respect to the response to treatment and the continuing need for treatment. After 12 months this evaluation should include suspension of Protopic treatment in paediatric patients (see section 4.2). The effect of treatment with Protopic ointment on the developing immune system of children aged below 2 years has not been established (see section 4.1).

Protopic contains the active substance tacrolimus, a calcineurin inhibitor. In transplant patients, prolonged systemic exposure to intense immunosuppression following systemic administration of calcineurin inhibitors has been associated with an increased risk of developing lymphomas and skin malignancies. Patients with atopic dermatitis treated with Protopic have not been found to have significant systemic tacrolimus levels and the role of local immunosuppression is unknown.
Based on the results of long-term studies and experience, a link between Protopic ointment treatment and development of malignancies has not been confirmed, but definitive conclusions cannot be drawn. It is recommended to use tacrolimus ointment at the lowest strength and the lowest frequency for the shortest duration necessary as determined by the physician's evaluation of the clinical condition (see section 4.2).

Lymphadenopathy was uncommonly (0.8%) reported in clinical trials. The majority of these cases were related to infections (skin, respiratory tract, tooth) and resolved with appropriate antibiotic therapy. Lymphadenopathy present at initiation of therapy should be investigated and kept under review. 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. Patients who develop lymphadenopathy during treatment should be monitored to ensure that the lymphadenopathy resolves.

Patients with atopic dermatitis are predisposed to superficial skin infections. 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. Treatment with Protopic is associated with an increased risk of folliculitis and herpes viral infections (herpes simplex dermatitis [eczema herpeticum], herpes simplex [cold sores], Kaposi's

varicelliform eruption) (see section 4.8). In the presence of these infections, the balance of risks and benefits associated with Protopic use should be evaluated.

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 agents.

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.

As with any topical medicinal product, 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 (see section 5.2).

Excipients warnings
Protopic ointment contains butylhydroxytoluene (E321) as an excipient, which may cause local skin reactions (e.g. contact dermatitis), or irritation to the eyes and mucous membranes.

4.5 Interaction with other medicinal products and other forms of interaction

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 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).

4.6 Fertility, Pregnancy and lactation

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.

Breast-feeding
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
There are no fertility data available.

4.7 Effects on ability to drive and use machines

Protopic ointment has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

In clinical studies approximately 50% of patients experienced some type of skin irritation adverse reaction at the site of application. Burning sensation and pruritus were very common, usually mild to moderate in severity and tended to resolve within one week of starting treatment. 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 may be at an increased risk of folliculitis, acne and herpes viral infections.

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 to <1/10) and uncommon (≥1/1,000 to <1/100). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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

Investigations				Drug level increased* (see section 4.4)

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

Maintenance treatment
In a study of maintenance treatment (twice weekly 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).

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

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Overdosage following topical administration is unlikely.
If ingested, general supportive measures may be appropriate. These may include monitoring of vital signs and observation of clinical status. Due to the nature of the ointment vehicle, induction of vomiting or gastric lavage is not recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Agents for dermatitis, excluding corticosteroids, ATC code: D11AH01

Mechanism of action and pharmacodynamic effects
The mechanism of action of tacrolimus in atopic dermatitis is not fully understood. While the following have been observed, the clinical significance of these observations in atopic dermatitis is not known.
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-α and IFN-γ.
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, basophils and eosinophils.

In animals, tacrolimus ointment suppressed inflammatory reactions in experimental and spontaneous dermatitis models that resemble human atopic dermatitis. Tacrolimus ointment did not reduce skin thickness and did not cause skin atrophy in animals.

In patients with atopic dermatitis, improvement of skin lesions during treatment with tacrolimus ointment was associated with reduced Fc receptor expression on Langerhans cells and a reduction of their hyperstimulatory activity towards T cells. Tacrolimus ointment does not affect collagen synthesis in humans.

Clinical efficacy and safety

The efficacy and safety of Protopic was assessed in more than 18,500 patients treated with tacrolimus ointment in Phase I to Phase III clinical trials. Data from six major trials are presented here.

In a six-month multicentre double-blind randomised trial, 0.1% tacrolimus ointment was administered twice-a-day to adults with moderate to severe atopic dermatitis and compared to a topical corticosteroid based regimen (0.1% hydrocortisone butyrate on trunk and extremities, 1% hydrocortisone acetate on face and neck). The primary endpoint was the response rate at month 3 defined as the proportion of patients with at least 60% improvement in the mEASI (modified Eczema Area and Severity Index) between baseline and month 3. The response rate in the 0.1% tacrolimus group (71.6%) was significantly higher than that in the topical corticosteroid based treatment group (50.8%; $p<0.001$; Table 1). The response rates at month 6 were comparable to the 3-month results.

Table 1: Efficacy at month 3

	Topical corticosteroid regimen§ (N=485)	Tacrolimus 0.1% (N=487)
Response rate of ≥ 60% improvement in mEASI (Primary Endpoint)§§	50.8%	71.6%
Improvement ≥ 90% in Physician's Global Evaluation	28.5%	47.7%

§ Topical corticosteroid regimen = 0.1% hydrocortisone butyrate on trunk and extremities, 1% hydrocortisone acetate on face and neck
§§ higher values = greater improvement

The incidence and nature of most adverse events were similar in the two treatment groups. Skin burning, herpes simplex, alcohol intolerance (facial flushing or skin sensitivity after alcohol intake), skin tingling, hyperaesthesia, acne and fungal dermatitis occurred more often in the tacrolimus treatment group. There were no clinically relevant changes in the laboratory values or vital signs in either treatment group throughout the study.

In the second trial, children aged from 2 to 15 years with moderate to severe atopic dermatitis received twice daily treatment for three weeks of 0.03% tacrolimus ointment, 0.1% tacrolimus ointment or 1% hydrocortisone acetate ointment. The primary endpoint was the area-under-the-curve (AUC) of the mEASI as a percentage of baseline averaged over the treatment period. The results of this multicentre, double-blind, randomised trial showed that tacrolimus ointment, 0.03% and 0.1%, is significantly more effective ($p<0.001$ for both) than 1% hydrocortisone acetate ointment (Table 2).

Table 2: Efficacy at week 3

	Hydrocortisone acetate 1% (N=185)	Tacrolimus 0.03% (N=189)	Tacrolimus 0.1% (N=186)
Median mEASI as Percentage of Baseline mean AUC (Primary Endpoint)§	64.0%	44.8%	39.8%
Improvement ≥ 90% in Physician's Global Evaluation	15.7%	38.5%	48.4%

§ lower values = greater improvement

The incidence of local skin burning was higher in the tacrolimus treatment groups than in the hydrocortisone group. Pruritus decreased over time in the tacrolimus groups but not in the hydrocortisone group. There were no clinically relevant changes in the laboratory values or vital signs in either treatment group throughout the clinical trial.

The purpose of the third multicentre, double-blind, randomised study was the assessment of efficacy and safety of 0.03% tacrolimus ointment applied once or twice a day relative to twice daily

administration of 1% hydrocortisone acetate ointment in children with moderate to severe atopic dermatitis. Treatment duration was for up to three weeks.

Table 3: Efficacy at week 3

	Hydrocortisone acetate 1% Twice daily (N=207)	Tacrolimus 0.03% Once daily (N=207)	Tacrolimus 0.03% Twice daily (N=210)
Median mEASI Percentage Decrease (Primary Endpoint)§	47.2%	70.0%	78.7%
Improvement ≥ 90% in Physician's Global Evaluation	13.6%	27.8%	36.7%

§ higher values = greater improvement

The primary endpoint was defined as the percentage decrease in mEASI from the baseline to end of treatment. A statistically significant better improvement was shown for once daily and twice daily 0.03% tacrolimus ointment compared to twice daily hydrocortisone acetate ointment ($p<0.001$ for both). Twice daily treatment with 0.03% tacrolimus ointment was more effective than once daily administration (Table 3). The incidence of local skin burning was higher in the tacrolimus treatment groups than in the hydrocortisone group. There were no clinically relevant changes in the laboratory values or vital signs in either treatment group throughout the study.

In the fourth trial, approximately 800 patients (aged ≥2 years) received 0.1% tacrolimus ointment intermittently or continuously in an open-label, long-term safety study for up to four years, with 300 patients receiving treatment for at least three years and 79 patients receiving treatment for a minimum of 42 months. Based on changes from baseline in EASI score and body surface area affected, patients regardless of age had improvement in their atopic dermatitis at all subsequent time points. In addition, there was no evidence of loss of efficacy throughout the duration of the clinical trial. The overall incidence of adverse events tended to decrease as the study progressed for all patients independent of age. The three most common adverse events reported were flu-like symptoms (cold, common cold, influenza, upper respiratory infection, etc.), pruritus and skin burning. No adverse events previously unreported in shorter duration and/or previous studies were observed in this long-term study.

The efficacy and safety of tacrolimus ointment in maintenance treatment of mild to severe atopic dermatitis was assessed in 524 patients in two Phase III multicentre clinical trials of similar design, one in adult patients (≥16 years) and one in paediatric patients (2-15 years). In both studies, patients with active disease entered an open-label period (OLP) during which they treated affected lesions with tacrolimus ointment twice daily until improvement had reached a predefined score (Investigator's Global Assessment [IGA] ≤2, i.e. clear, almost clear or mild disease) for a maximum of 6 weeks. Thereafter, patients entered a double-blind disease control period (DCP) for up to 12 months. Patients were randomised to receive either tacrolimus ointment (0.1% adults; 0.03% children) or vehicle, once a day twice weekly on Mondays and Thursdays. If a disease exacerbation occurred, patients were treated with open-label tacrolimus ointment twice daily for a maximum of 6 weeks until the IGA score returned to ≤2.
The primary endpoint in both studies was the number of disease exacerbations requiring a "substantial therapeutic intervention" during the DCP, defined as an exacerbation with an IGA of 3-5 (i.e. moderate, severe and very severe disease) on the first day of the flare, and requiring more than 7 days treatment. Both studies showed significant benefit with twice weekly treatment with tacrolimus ointment with regard to the primary and key secondary endpoints over a period of 12 months in a pooled population of patients with mild to severe atopic dermatitis. In a subanalysis of a pooled population of patients with moderate to severe atopic dermatitis these differences remained statistically significant (Table 4). No adverse events not reported previously were observed in these studies.

Table 4: Efficacy (moderate to severe subpopulation)

	Adults, ≥16 years		Children, 2-15 years	
	Tacrolimus 0.1% Twice weekly (N=80)	Vehicle Twice weekly (N=73)	Tacrolimus 0.03% Twice weekly (N=78)	Vehicle Twice weekly (N=75)
Median number of DEs requiring substantial intervention adjusted for time at risk (% of patients without DE requiring substantial intervention)	1.0 (48.8%)	5.3 (17.8%)	1.0 (46.2%)	2.9 (21.3%)
Median time to first DE requiring substantial intervention	142 days	15 days	217 days	36 days
Median number of DEs adjusted for time at risk (% of patients without any DE periods)	1.0 (42.5%)	6.8 (12.3%)	1.5 (41.0%)	3.5 (14.7%)
Median time to first DE	123 days	14 days	146 days	17 days
Mean (SD) percentage of days of DE exacerbation treatment	16.1 (23.6)	39.0 (27.8)	16.9 (22.1)	29.9 (26.8)

DE: disease exacerbation
P<0.001 in favour of tacrolimus ointment 0.1% (adults) and 0.03% (children) for the primary and key secondary endpoints

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.

5.2 Pharmacokinetic properties

Clinical data have shown that tacrolimus 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.
Target trough concentrations for systemic immunosuppression for oral tacrolimus are 5-20 ng/mL in transplant patients. Most atopic dermatitis patients (adults and children) treated with single or repeated application of tacrolimus ointment (0.03-0.1%), and infants from age of 5 months treated with tacrolimus ointment (0.03%) 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. However, both the extent and the rate of topical absorption of tacrolimus decrease as the skin heals. In both adults and children with an average of 50% body surface area treated, systemic exposure (i.e. AUC) of tacrolimus from Protopic ointment is approximately 30-fold less than that 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
As systemic exposure is low with tacrolimus ointment, the high binding of tacrolimus (>98.8%) to plasma proteins is considered not to be clinically relevant.
Following topical application of tacrolimus ointment, tacrolimus is selectively delivered to the skin with minimal diffusion into the systemic circulation.

Biotransformation
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 l/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, with minimal systemic exposure and no evidence of accumulation (see above).

5.3 Preclinical safety data

Repeated dose toxicity and local tolerance
Repeated topical administration of tacrolimus ointment or the ointment vehicle to rats, rabbits and micropigs was associated with slight dermal changes such as erythema, oedema and papules.
Long-term topical treatment of rats with tacrolimus led to systemic toxicity including alterations of kidneys, pancreas, eyes and nervous system. The changes were caused by high systemic exposure of rodents resulting from high transdermal absorption of tacrolimus. Slightly lower body weight gain in females was the only systemic change observed in micropigs at high ointment concentrations (3%).
Rabbits were shown to be especially sensitive to intravenous administration of tacrolimus, reversible cardiotoxic effects being observed.

Mutagenicity
In vitro and *in vivo* tests did not indicate a genotoxic potential of tacrolimus.

Carcinogenicity
Systemic carcinogenicity studies in mice (18 months) and rats (24 months) revealed no carcinogenic potential of tacrolimus.
In a 24-month dermal carcinogenicity study performed in mice with 0.1% ointment, no skin tumours were observed. In the same study an increased incidence of lymphoma was detected in association with high systemic exposure.
In a photocarcinogenicity study, albino hairless mice were chronically treated with tacrolimus ointment and UV radiation. Animals treated with tacrolimus ointment showed a statistically significant reduction in time to skin tumour (squamous cell carcinoma) development and an increase in the number of tumours. This effect occurred at the higher concentrations of 0.3% and 1%. The relevance to humans is currently unknown. It is unclear whether the effect of tacrolimus is due to systemic immunosuppression or a local effect. The risk for humans cannot be completely ruled out as the potential for local immunosuppression with the long-term use of tacrolimus ointment is unknown.

Reproduction toxicity
Embryo/foetal toxicity was observed in rats and rabbits, but only at doses that caused significant toxicity in maternal animals. Reduced sperm function was noted in male rats at high subcutaneous doses of tacrolimus.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

White soft paraffin
Liquid paraffin
Propylene carbonate
White beeswax
Hard paraffin
Butylhydroxytoluene (E321)
All-*rac*-α-tocopherol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Laminate tube with an inner lining of low-density-polyethylene fitted with a white polypropylene screw cap.

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

LEO Pharma A/S
Industriparken 55
2750 Ballerup
Denmark

8. MARKETING AUTHORISATION NUMBERS

EU/1/02/201/001
EU/1/02/201/002
EU/1/02/201/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 February 2002
Date of latest renewal: 20 November 2006

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Protopic 0.1% ointment

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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Excipient with known effect
Butylhydroxytoluene (E321) 15 micrograms/g ointment.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Ointment

A white to slightly yellowish ointment.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Protopic 0.1 % ointment is indicated in adults and adolescents (16 years of age and above)

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.

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).

4.2 Posology and method of administration

Protopic treatment should be initiated by physicians with experience in the diagnosis and treatment of atopic dermatitis.

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

Paediatric population
Only Protopic 0.03 % ointment should be used in children from the age of 2 to 16 years.
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 (16 years of age and above) 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.

If signs of a flare reoccur, twice daily treatment should be re-initiated (see flare treatment section above).

Elderly
Specific studies have not been conducted in older people (see flare treatment section above).

Paediatric population
Only Protopic 0.03 % ointment should be used in children from the age of 2 to 16 years.
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).

4.3 Contraindications

Hypersensitivity to the active substance, macrolides in general, or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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 (see section 5.3). Physicians 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. The development of any new change different from previous eczema within a treated area should be reviewed by the physician.

The use of tacrolimus ointment is not recommended in patients with a skin barrier defect, such as Netherton's syndrome, lamellar ichthyosis, generalized erythroderma, pyoderma gangrenosum or cutaneous Graft Versus Host Disease. These skin conditions may increase systemic absorption of tacrolimus. Post-marketing cases of increased tacrolimus blood level have been reported in these conditions. Protopic should not be used in patients with congenital or acquired immunodeficiencies or in patients on therapy that cause immunosuppression.

Care should be exercised if applying Protopic to patients with extensive skin involvement over an extended period of time, especially in children (see section 4.2). Patients, particularly paediatric patients should be continuously evaluated during treatment with Protopic with respect to the response to treatment and the continuing need for treatment. After 12 months this evaluation should include suspension of Protopic treatment in paediatric patients (see section 4.2).

Protopic contains the active substance tacrolimus, a calcineurin inhibitor. In transplant patients, prolonged systemic exposure to intense immunosuppression following systemic administration of calcineurin inhibitors has been associated with an increased risk of developing lymphomas and skin malignancies. Patients with atopic dermatitis treated with Protopic have not been found to have significant systemic tacrolimus levels and the role of local immunosuppression is unknown.
Based on the results of long-term studies and experience, a link between Protopic ointment treatment and development of malignancies has not been confirmed, but definitive conclusions cannot be drawn. It is recommended to use tacrolimus ointment at the lowest strength and the lowest frequency for the shortest duration necessary as determined by the physician's evaluation of the clinical condition (see section 4.2).

Lymphadenopathy was uncommonly (0.8%) reported in clinical trials. The majority of these cases were related to infections (skin, respiratory tract, tooth) and resolved with appropriate antibiotic therapy. Lymphadenopathy present at initiation of therapy should be investigated and kept under review. 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. Patients who develop lymphadenopathy during treatment should be monitored to ensure that the lymphadenopathy resolves.

Patients with atopic dermatitis are predisposed to superficial skin infections. 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. Treatment with Protopic is associated with an increased risk of folliculitis and herpes viral infections (herpes simplex dermatitis [eczema herpeticum], herpes simplex [cold sores], Kaposi's varicelliform eruption) (see section 4.8). In the presence of these infections, the balance of risks and benefits associated with Protopic use should be evaluated.

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 agents.

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.

As with any topical medicinal product, 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 (see section 5.2).

Excipients warnings
Protopic ointment contains butylhydroxytoluene (E321) as an excipient, which may cause local skin reactions (e.g. contact dermatitis), or irritation to the eyes and mucous membranes.

4.5 Interaction with other medicinal products and other forms of interaction

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 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).

4.6 Fertility, Pregnancy and lactation

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.

Breast-feeding
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
There are no fertility data available.

4.7 Effects on ability to drive and use machines

Protopic ointment has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

In clinical studies approximately 50% of patients experienced some type of skin irritation adverse reaction at the site of application. Burning sensation and pruritus were very common, usually mild to moderate in severity and tended to resolve within one week of starting treatment. 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 may be at an increased risk of folliculitis, acne and herpes viral infections.

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 to <1/10) and uncommon (≥1/1,000 to <1/100). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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*		Ophthalmic Herpes Infection*
Metabolism and nutrition disorders		Alcohol intolerance (facial flushing or skin irritation after consumption of an alcoholic beverage)		
Nervous system disorders		Paraesthesias and dysaesthesias (hyperaesthesia, burning sensation)		
Skin and subcutaneous tissue disorders		Pruritus	Acne*	Rosacea* Lentigo*
General disorders and administration site conditions	Application site burning, Application site pruritus	Application site warmth, Application site erythema, Application site pain, Application site irritation, Application site paraesthesia, Application site rash		Application site oedema*
Investigations				Drug level increased* (see section 4.4)

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

Maintenance treatment
In a study of maintenance treatment (twice weekly 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).

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Overdosage following topical administration is unlikely.
If ingested, general supportive measures may be appropriate. These may include monitoring of vital signs and observation of clinical status. Due to the nature of the ointment vehicle, induction of vomiting or gastric lavage is not recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Agents for dermatitis, excluding corticosteroids, ATC code: D11AH01

Mechanism of action and pharmacodynamic effects
The mechanism of action of tacrolimus in atopic dermatitis is not fully understood. While the following have been observed, the clinical significance of these observations in atopic dermatitis is not known.
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-α and IFN-γ.
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, basophils and eosinophils.

In animals, tacrolimus ointment suppressed inflammatory reactions in experimental and spontaneous dermatitis models that resemble human atopic dermatitis. Tacrolimus ointment did not reduce skin thickness and did not cause skin atrophy in animals.

In patients with atopic dermatitis, improvement of skin lesions during treatment with tacrolimus ointment was associated with reduced Fc receptor expression on Langerhans cells and a reduction of their hyperstimulatory activity towards T cells. Tacrolimus ointment does not affect collagen synthesis in humans.

Clinical efficacy and safety
The efficacy and safety of Protopic was assessed in more than 18,500 patients treated with tacrolimus ointment in Phase I to Phase III clinical trials. Data from six major trials are presented here.

In a six-month multicentre double-blind randomised trial, 0.1% tacrolimus ointment was administered twice-a-day to adults with moderate to severe atopic dermatitis and compared to a topical corticosteroid based regimen (0.1% hydrocortisone butyrate on trunk and extremities, 1% hydrocortisone acetate on face and neck). The primary endpoint was the response rate at month 3 defined as the proportion of patients with at least 60% improvement in the mEASI (modified Eczema Area and Severity Index) between baseline and month 3. The response rate in the 0.1% tacrolimus group (71.6%) was significantly higher than that in the topical corticosteroid based treatment group (50.8%; $p<0.001$; Table 1). The response rates at month 6 were comparable to the 3-month results.

Table 1: Efficacy at month 3

	Topical corticosteroid regimen§ (N=485)	Tacrolimus 0.1% (N=487)
Response rate of ≥ 60% improvement in mEASI (Primary Endpoint)§§	50.8%	71.6%
Improvement ≥ 90% in Physician's Global Evaluation	28.5%	47.7%

§ Topical corticosteroid regimen = 0.1% hydrocortisone butyrate on trunk and extremities, 1% hydrocortisone acetate on face and neck
§§ higher values = greater improvement

The incidence and nature of most adverse events were similar in the two treatment groups. Skin burning, herpes simplex, alcohol intolerance (facial flushing or skin sensitivity after alcohol intake), skin tingling, hyperaesthesia, acne and fungal dermatitis occurred more often in the tacrolimus treatment group. There were no clinically relevant changes in the laboratory values or vital signs in either treatment group throughout the study.

In the second trial, children aged from 2 to 15 years with moderate to severe atopic dermatitis received twice daily treatment for three weeks of 0.03% tacrolimus ointment, 0.1% tacrolimus ointment or 1% hydrocortisone acetate ointment. The primary endpoint was the area-under-the-curve (AUC) of the mEASI as a percentage of baseline averaged over the treatment period. The results of this multicentre, double-blind, randomised trial showed that tacrolimus ointment, 0.03% and 0.1%, is significantly more effective ($p<0.001$ for both) than 1% hydrocortisone acetate ointment (Table 2).

Table 2: Efficacy at week 3

	Hydrocortisone acetate 1% (N=185)	Tacrolimus 0.03% (N=189)	Tacrolimus 0.1% (N=186)
Median mEASI as Percentage of Baseline mean AUC (Primary Endpoint)§	64.0%	44.8%	39.8%
Improvement ≥ 90% in Physician's Global Evaluation	15.7%	38.5%	48.4%

§ lower values = greater improvement

The incidence of local skin burning was higher in the tacrolimus treatment groups than in the hydrocortisone group. Pruritus decreased over time in the tacrolimus groups but not in the hydrocortisone group. There were no clinically relevant changes in the laboratory values or vital signs in either treatment group throughout the clinical trial.

The purpose of the third multicentre, double-blind, randomised study was the assessment of efficacy and safety of 0.03% tacrolimus ointment applied once or twice a day relative to twice daily administration of 1% hydrocortisone acetate ointment in children with moderate to severe atopic dermatitis. Treatment duration was for up to three weeks.

Table 3: Efficacy at week 3

	Hydrocortisone acetate 1% Twice daily (N=207)	Tacrolimus 0.03% Once daily (N=207)	Tacrolimus 0.03% Twice daily (N=210)
Median mEASI Percentage Decrease (Primary Endpoint)§	47.2%	70.0%	78.7%
Improvement ≥90% in Physician's Global Evaluation	13.6%	27.8%	36.7%

§ higher values = greater improvement

The primary endpoint was defined as the percentage decrease in mEASI from the baseline to end of treatment. A statistically significant better improvement was shown for once daily and twice daily 0.03% tacrolimus ointment compared to twice daily hydrocortisone acetate ointment ($p<0.001$ for both). Twice daily treatment with 0.03% tacrolimus ointment was more effective than once daily administration (Table 3). The incidence of local skin burning was higher in the tacrolimus treatment groups than in the hydrocortisone group. There were no clinically relevant changes in the laboratory values or vital signs in either treatment group throughout the study.

In the fourth trial, approximately 800 patients (aged ≥2 years) received 0.1% tacrolimus ointment intermittently or continuously in an open-label, long-term safety study for up to four years, with 300 patients receiving treatment for at least three years and 79 patients receiving treatment for a minimum of 42 months. Based on changes from baseline in EASI score and body surface area affected, patients regardless of age had improvement in their atopic dermatitis at all subsequent time points. In addition, there was no evidence of loss of efficacy throughout the duration of the clinical trial. The overall incidence of adverse events tended to decrease as the study progressed for all patients independent of age. The three most common adverse events reported were flu-like symptoms (cold, common cold, influenza, upper respiratory infection, etc.), pruritus and skin burning. No adverse events previously unreported in shorter duration and/or previous studies were observed in this long-term study.

The efficacy and safety of tacrolimus ointment in maintenance treatment of mild to severe atopic dermatitis was assessed in 524 patients in two Phase III multicentre clinical trials of similar design, one in adult patients (≥16 years) and one in paediatric patients (2-15 years). In both studies, patients with active disease entered an open-label period (OLP) during which they treated affected lesions with tacrolimus ointment twice daily until improvement had reached a predefined score (Investigator's Global Assessment [IGA] ≤ 2, i.e. clear, almost clear or mild disease) for a maximum of 6 weeks. Thereafter, patients entered a double-blind disease control period (DCP) for up to 12 months. Patients were randomised to receive either tacrolimus ointment (0.1% adults; 0.03% children) or vehicle, once a day twice weekly on Mondays and Thursdays. If a disease exacerbation occurred, patients were treated with open-label tacrolimus ointment twice daily for a maximum of 6 weeks until the IGA score returned to ≤2.
The primary endpoint in both studies was the number of disease exacerbations requiring a "substantial therapeutic intervention" during the DCP, defined as an exacerbation with an IGA of 3-5 (i.e. moderate, severe and very severe disease) on the first day of the flare, and requiring more than 7 days treatment. Both studies showed significant benefit with twice weekly treatment with tacrolimus ointment with regard to the primary and key secondary endpoints over a period of 12 months in a pooled population of patients with mild to severe atopic dermatitis. In a subanalysis of a pooled population of patients with moderate to severe atopic dermatitis these differences remained statistically significant (Table 4). No adverse events not reported previously were observed in these studies.

Table 4: Efficacy (moderate to severe subpopulation)

	Adults, ≥16 years		Children, 2-15 years	
	Tacrolimus 0.1% Twice weekly (N=80)	Vehicle Twice weekly (N=73)	Tacrolimus 0.03% Twice weekly (N=78)	Vehicle Twice weekly (N=75)
Median number of DEs requiring substantial intervention adjusted for time at risk (% of patients without DE requiring substantial intervention)	1.0 (48.8%)	5.3 (17.8%)	1.0 (46.2%)	2.9 (21.3%)
Median time to first DE requiring substantial intervention	142 days	15 days	217 days	36 days

Median number of DEs adjusted for time at risk (% of patients without any DE periods)	1.0 (42.5%)	6.8 (12.3%)	1.5 (41.0%)	3.5 (14.7%)
Median time to first DE	123 days	14 days	146 days	17 days
Mean (SD) percentage of days of DE exacerbation treatment	16.1 (23.6)	39.0 (27.8)	16.9 (22.1)	29.9 (26.8)

DE: disease exacerbation
P<0.001 in favour of tacrolimus ointment 0.1% (adults) and 0.03% (children) for the primary and key secondary endpoints

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.

5.2 Pharmacokinetic properties

Clinical data have shown that tacrolimus 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.
Target trough concentrations for systemic immunosuppression for oral tacrolimus are 5-20 ng/mL in transplant patients. Most atopic dermatitis patients (adults and children) treated with single or repeated application of tacrolimus ointment (0.03-0.1%), and infants from age of 5 months treated with tacrolimus ointment (0.03%) 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. However, both the extent and the rate of topical absorption of tacrolimus decrease as the skin heals. In both adults and children with an average of 50% body surface area treated, systemic exposure (i.e. AUC) of tacrolimus from Protopic ointment is approximately 30-fold less than that 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
As systemic exposure is low with tacrolimus ointment, the high binding of tacrolimus (>98.8%) to plasma proteins is considered not to be clinically relevant.
Following topical application of tacrolimus ointment, tacrolimus is selectively delivered to the skin with minimal diffusion into the systemic circulation.

Biotransformation
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 l/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, with minimal systemic exposure and no evidence of accumulation (see above).

5.3 Preclinical safety data

Repeated dose toxicity and local tolerance
Repeated topical administration of tacrolimus ointment or the ointment vehicle to rats, rabbits and micropigs was associated with slight dermal changes such as erythema, oedema and papules.
Long-term topical treatment of rats with tacrolimus led to systemic toxicity including alterations of kidneys, pancreas, eyes and nervous system. The changes were caused by high systemic exposure of rodents resulting from high transdermal absorption of tacrolimus. Slightly lower body weight gain in females was the only systemic change observed in micropigs at high ointment concentrations (3%). Rabbits were shown to be especially sensitive to intravenous administration of tacrolimus, reversible cardiotoxic effects being observed.

Mutagenicity
In vitro and *in vivo* tests did not indicate a genotoxic potential of tacrolimus.

Carcinogenicity
Systemic carcinogenicity studies in mice (18 months) and rats (24 months) revealed no carcinogenic potential of tacrolimus.
In a 24-month dermal carcinogenicity study performed in mice with 0.1% ointment, no skin tumours were observed. In the same study an increased incidence of lymphoma was detected in association with high systemic exposure.
In a photocarcinogenicity study, albino hairless mice were chronically treated with tacrolimus ointment and UV radiation. Animals treated with tacrolimus ointment showed a statistically significant reduction in time to skin tumour (squamous cell carcinoma) development and an increase in the number of tumours. This effect occurred at the higher concentrations of 0.3% and 1%. The relevance to humans is currently unknown. It is unclear whether the effect of tacrolimus is due to systemic immunosuppression or a local effect. The risk for humans cannot be completely ruled out as the potential for local immunosuppression with the long-term use of tacrolimus ointment is unknown.

Reproduction toxicity
Embryo/foetal toxicity was observed in rats and rabbits, but only at doses that caused significant toxicity in maternal animals. Reduced sperm function was noted in male rats at high subcutaneous doses of tacrolimus.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

White soft paraffin
Liquid paraffin
Propylene carbonate
White beeswax
Hard paraffin

Butylhydroxytoluene (E321)
All-*rac*-α-tocopherol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Laminate tube with an inner lining of low-density-polyethylene fitted with a white polypropylene screw cap.

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

LEO Pharma A/S
Industriparken 55
2750 Ballerup
Denmark

8. MARKETING AUTHORISATION NUMBERS

EU/1/02/201/003
EU/1/02/201/004
EU/1/02/201/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 February 2002
Date of latest renewal: 20 November 2006

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Astellas Ireland Co. Ltd.
Killorglin
County Kerry
Ireland

LEO Laboratories Ltd.
285 Cashel Road
Crumlin, Dublin 12
Ireland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRUCTIONS WITH REGARD TO THE SAFE AND EFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorization holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PROTOPIC 0.03% OINTMENT (10 g, 30 g, 60 g CARTON)

1. NAME OF THE MEDICINAL PRODUCT

Protopic 0.03% ointment
tacrolimus monohydrate

2. STATEMENT OF ACTIVE SUBSTANCE

1 g ointment contains: 0.3 mg tacrolimus (as monohydrate)

3. LIST OF EXCIPIENTS

white soft paraffin, liquid paraffin, propylene carbonate, white beeswax, hard paraffin, butylhydroxytoluene (E321), all-*rac*-α-tocopherol.

4. PHARMACEUTICAL FORM AND CONTENTS

Ointment

10 g
30 g
60 g

5. METHOD AND ROUTE OF ADMINISTRATION

Cutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

LEO Pharma A/S
Industriparken 55
2750 Ballerup
Denmark

12. MARKETING AUTHORISATION NUMBERS

EU/1/02/201/005 10 g
EU/1/02/201/001 30 g
EU/1/02/201/002 60 g

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Protopic 0.03%

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PROTOPIC 0.03% OINTMENT (10 g TUBE)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Protopic 0.03% ointment
tacrolimus monohydrate
Cutaneous use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 g

6. OTHER

Keep out of the sight and reach of children.

Do not store above 25°C.

EU/1/02/201/005

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

PROTOPIC 0.03% OINTMENT (30 g, 60 g TUBE)

1. NAME OF THE MEDICINAL PRODUCT

Protopic 0.03% ointment
tacrolimus monohydrate

2. STATEMENT OF ACTIVE SUBSTANCE

1 g ointment contains: 0.3 mg tacrolimus (as monohydrate)

3. LIST OF EXCIPIENTS

white soft paraffin, liquid paraffin, propylene carbonate, white beeswax, hard paraffin, butylhydroxytoluene (E321), all-*rac*-α-tocopherol.

4. PHARMACEUTICAL FORM AND CONTENTS

Ointment

30 g
60 g

5. METHOD AND ROUTE OF ADMINISTRATION

Cutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

LEO Pharma A/S
Industriparken 55
2750 Ballerup
Denmark

12. MARKETING AUTHORISATION NUMBERS

EU/1/02/201/001 30 g
EU/1/02/201/002 60 g

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PROTOPIC 0.1% OINTMENT (10 g, 30 g, 60 g CARTON)

1. NAME OF THE MEDICINAL PRODUCT

Protopic 0.1% ointment
tacrolimus monohydrate

2. STATEMENT OF ACTIVE SUBSTANCE

1 g ointment contains: 1.0 mg tacrolimus (as monohydrate)

3. LIST OF EXCIPIENTS

white soft paraffin, liquid paraffin, propylene carbonate, white beeswax, hard paraffin, butylhydroxytoluene (E321), all-*rac*-α-tocopherol.

4. PHARMACEUTICAL FORM AND CONTENTS

Ointment

10 g
30 g
60 g

5. METHOD AND ROUTE OF ADMINISTRATION

Cutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

LEO Pharma A/S
Industriparken 55
2750 Ballerup
Denmark

12. MARKETING AUTHORISATION NUMBERS

EU/1/02/201/006 10 g
EU/1/02/201/003 30 g
EU/1/02/201/004 60 g

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Protopic 0.1%

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PROTOPIC 0.1% OINTMENT (10 g TUBE)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Protopic 0.1% ointment
tacrolimus monohydrate
Cutaneous use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 g

6. OTHER

Keep out of the sight and reach of children.

Do not store above 25°C.

EU/1/02/201/006

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

PROTOPIC 0.1% OINTMENT (30 g, 60 g TUBE)

1. NAME OF THE MEDICINAL PRODUCT

Protopic 0.1% ointment
tacrolimus monohydrate

2. STATEMENT OF ACTIVE SUBSTANCE

1 g ointment contains: 1.0 mg tacrolimus (as monohydrate)

3. LIST OF EXCIPIENTS

white soft paraffin, liquid paraffin, propylene carbonate, white beeswax, hard paraffin, butylhydroxytoluene (E321), all-*rac*-α-tocopherol.

4. PHARMACEUTICAL FORM AND CONTENTS

Ointment

30 g
60 g

5. METHOD AND ROUTE OF ADMINISTRATION

Cutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

LEO Pharma A/S
Industriparken 55
2750 Ballerup
Denmark

12. MARKETING AUTHORISATION NUMBERS

EU/1/02/201/003 30 g
EU/1/02/201/004 60 g

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Protopic 0.03% ointment
tacrolimus monohydrate

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Protopic is and what it is used for

The active substance of Protopic, tacrolimus monohydrate, is an immunomodulating agent.

Protopic 0.03% ointment is used to treat moderate to severe atopic dermatitis (eczema) in adults who are not adequately responsive to or are intolerant of conventional therapies such as topical corticosteroids and in children (2 years of age and older) who failed to respond adequately to conventional therapies such as topical corticosteroids.

Once moderate to severe atopic dermatitis is cleared or almost cleared after up to 6 weeks treatment of a flare, and if you are experiencing frequent flares (i.e. 4 or more per year), it may be possible to prevent flares coming back or prolong the time you are free from flares by using Protopic 0.03% ointment twice weekly.

In atopic dermatitis, an over-reaction of the skin's immune system causes skin inflammation (itchiness, redness, dryness). Protopic alters the abnormal immune response and relieves the skin inflammation and the itch.

2. What you need to know before you use Protopic

Do not use Protopic
- If you are allergic to tacrolimus or any of the other ingredients of this medicine (listed in section 6) or to macrolide antibiotics (e.g. azithromycin, clarithromycin, erythromycin).

Warnings and precautions
Talk to your doctor before using Protopic:
- If you have **liver failure**.
- If you have any **skin malignancies** (tumours) or if you have a **weakened immune system** (immuno-compromised) whatever the cause.
- If you have an **inherited skin barrier disease** such as Netherton's syndrome, lamellar ichthyosis (extensive scaling of the skin due to a thickening of the outer layer of the skin), or if

you have an inflammatory skin disease such as pyoderma gangrenosum, or if you suffer from **generalised erythroderma** (inflammatory reddening and scaling of the entire skin).
- If you have a cutaneous Graft Versus Host Disease (an immune reaction of the skin which is a common complication in patients who have undergone a bone marrow transplant).
- If you have **swollen lymph nodes** at initiation of treatment. If your lymph nodes become swollen during treatment with Protopic, consult your doctor.
- If you have **infected lesions**. Do not apply the ointment to infected lesions.
- If you notice any **change to the appearance of your skin**, please inform your physician.
- Based on the results of long-term studies and experience, a link between Protopic ointment treatment and the development of malignancies has not been confirmed, but definitive conclusions cannot be drawn.
- Avoid exposing the skin to long periods of sunlight or artificial sunlight such as tanning beds. If you spend time outdoors after applying Protopic, use a sunscreen and wear loose fitting clothing that protects the skin from the sun. In addition, ask your doctor for advice on other appropriate sun protection methods. If you are prescribed light therapy, inform your doctor that you are using Protopic as it is not recommended to use Protopic and light therapy at the same time.
- If your doctor tells you to use Protopic twice weekly to keep your atopic dermatitis cleared, your condition should be reviewed by your doctor at least every 12 months, even if it remains under control. In children, maintenance treatment should be suspended after 12 months, to assess whether the need for continued treatment still exists.
- It is recommended to use Protopic ointment at the lowest possible strength, at the lowest frequency and for the shortest possible duration necessary. This decision should be based on your doctor's assessment of how your eczema responds to Protopic ointment.

Children
- Protopic ointment is **not approved for children younger than 2 years of age**. Therefore it should not be used in this age group. Please consult your doctor.
- The effect of treatment with Protopic on the developing immune system in children, especially the young, has not been established.

Other medicines, cosmetics and Protopic
Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines.

You may use moisturising creams and lotions during treatment with Protopic but these products should not be used within two hours of applying Protopic.

The use of Protopic at the same time as other preparations to be used on the skin or while taking oral corticosteroids (e.g. cortisone) or medicines which affect the immune system has not been studied.

Protopic with alcohol
While using Protopic, drinking alcohol may cause the skin or face to become flushed or red and feel hot.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Protopic contains butylhydroxytoluene (E321)
Protopic contains butylhydroxytoluene (E321), which may cause local skin reactions (e.g. contact dermatitis), or irritation to the eyes and mucous membranes.

3. How to use Protopic

Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

- Apply Protopic as a thin layer to affected areas of your skin.
- Protopic may be used on most parts of the body, including the face and neck and in the creases of your elbows and knees.
- Avoid using the ointment inside your nose or mouth or in your eyes. If the ointment gets on any of these areas, it should be thoroughly wiped off and/or rinsed off with water.
- Do not cover the skin being treated with bandages or wraps.
- Wash your hands after applying Protopic unless your hands are also being treated.
- Before applying Protopic after a bath or shower, be sure your skin is completely dry.

Children (2 years of age and older)
Apply Protopic 0.03 % ointment twice a day for up to three weeks, once in the morning and once in the evening. Afterwards the ointment should be used once a day on each affected region of the skin until the eczema has gone away.

Adults (16 years of age and older)
Two strengths of Protopic (Protopic 0.03% and Protopic 0.1% ointment) are available for adult patients (16 years of age and older). Your doctor will decide which strength is best for you.

Usually, treatment is started with Protopic 0.1% ointment twice a day, once in the morning and once in the evening, until the eczema has cleared. Depending on the response of your eczema your doctor will decide if the frequency of application can be reduced or the lower strength, Protopic 0.03% ointment, can be used.

Treat each affected region of your skin until the eczema has gone away. Improvement is usually seen within one week. If you do not see any improvement after two weeks, see your doctor about other possible treatments.

You may be told by your doctor to use Protopic ointment twice weekly once your atopic dermatitis has cleared or almost cleared (Protopic 0.03% for children and Protopic 0.1% for adults). Protopic ointment should be applied once a day twice weekly (e.g. Monday and Thursday) to areas of your body commonly affected by atopic dermatitis. There should be 2–3 days without Protopic treatment between applications.
If symptoms reappear you should use Protopic twice daily as outlined above and arrange to see your doctor to review your treatment.

If you accidentally swallow some ointment
If you accidentally swallow the ointment, consult your doctor or pharmacist as soon as possible. Do not try to induce vomiting.

If you forget to use Protopic
If you forget to apply the ointment at the scheduled time, do it as soon as you remember and then continue as before.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Very common (may affect more than 1 in 10 people):
- burning sensation and itching

These symptoms are usually mild to moderate and generally go away within one week of using Protopic.

Common (may affect up to 1 in 10 people):

- redness
- feeling of warmth
- pain
- increased skin sensitivity (especially to hot and cold)
- skin tingling
- rash
- local skin infection regardless of specific cause including but not limited to: inflamed or infected hair follicles, cold sores, generalised herpes simplex infections
- facial flushing or skin irritation after drinking alcohol is also common

Uncommon (may affect fewer than 1 in 100 people):
- acne

Following twice-weekly treatment application site infections have been reported in children and adults. Impetigo, a superficial bacterial skin infection that usually produces blisters or sores on skin, has been reported in children.

Rosacea (facial redness), rosacea-like dermatitis, lentigo (presence of flat brown spots on the skin), oedema at the application site and herpes eye infections have been reported during post-marketing experience.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Protopic

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the tube and carton after EXP. The expiry date refers to the last day of that month.
Do not store above 25ºC.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Protopic contains
- The active substance is tacrolimus monohydrate.
  One gram of Protopic 0.03% ointment contains 0.3 mg tacrolimus (as tacrolimus monohydrate).
- The other ingredients are white soft paraffin, liquid paraffin, propylene carbonate, white beeswax, hard paraffin, butylhydroxytoluene (E321) and all-*rac*-α-tocopherol.

What Protopic looks like and contents of the pack
Protopic is a white to slightly yellowish ointment. It is supplied in tubes containing 10, 30 or 60 grams of ointment. Not all pack sizes may be marketed. Protopic is available in two strengths (Protopic 0.03% and Protopic 0.1% ointment).

Marketing Authorisation Holder
LEO Pharma A/S
Industriparken 55

2750 Ballerup
Denmark

Manufacturer
Astellas Ireland Co. Ltd.
Killorglin
County Kerry
Ireland

LEO Laboratories Ltd.
285 Cashel Road
Crumlin, Dublin 12
Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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LEO Pharma Oy
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LEO Pharma AB
Tel: +46 40 3522 00

United Kingdom (Northern Ireland)
LEO Laboratories Ltd
Tel: +44 (0) 1844 347333

This leaflet was last revised in.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Package leaflet: Information for the user

Protopic 0.1% ointment
tacrolimus monohydrate

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Protopic is and what it is used for

The active substance of Protopic, tacrolimus monohydrate, is an immunomodulating agent.

Protopic 0.1% ointment is used to treat moderate to severe atopic dermatitis (eczema) in adults who are not adequately responsive to or are intolerant of conventional therapies such as topical corticosteroids.

Once moderate to severe atopic dermatitis is cleared or almost cleared after up to 6 weeks treatment of a flare, and if you are experiencing frequent flares (i.e. 4 or more per year), it may be possible to prevent flares coming back or prolong the time you are free from flares by using Protopic 0.1% ointment twice weekly.

In atopic dermatitis, an over-reaction of the skin's immune system causes skin inflammation (itchiness, redness, dryness). Protopic alters the abnormal immune response and relieves the skin inflammation and the itch.

2. What you need to know before you use Protopic

Do not use Protopic
- If you are allergic to tacrolimus or any of the other ingredients of this medicine (listed in section 6) or to macrolide antibiotics (e.g. azithromycin, clarithromycin, erythromycin).

Warnings and precautions
Talk to your doctor before using Protopic:
- If you have **liver failure**.
- If you have any **skin malignancies** (tumours) or if you have a **weakened immune system** (immuno-compromised) whatever the cause.
- If you have an **inherited skin barrier disease** such as Netherton's syndrome, lamellar ichthyosis (extensive scaling of the skin due to a thickening of the outer layer of the skin), or if you have an inflammatory skin disease such as pyoderma gangrenosum, or if you suffer from **generalised erythroderma** (inflammatory reddening and scaling of the entire skin).

- If you have a cutaneous Graft Versus Host Disease (an immune reaction of the skin which is a common complication in patients who have undergone a bone marrow transplant).
- If you have **swollen lymph nodes** at initiation of treatment. If your lymph nodes become swollen during treatment with Protopic, consult your doctor.
- If you have **infected lesions**. Do not apply the ointment to infected lesions.
- If you notice any **change to the appearance of your skin**, please inform your physician.
- Based on the results of long-term studies and experience, a link between Protopic ointment treatment and the development of malignancies has not been confirmed, but definitive conclusions cannot be drawn.
- Avoid exposing the skin to long periods of sunlight or artificial sunlight such as tanning beds. If you spend time outdoors after applying Protopic, use a sunscreen and wear loose fitting clothing that protects the skin from the sun. In addition, ask your doctor for advice on other appropriate sun protection methods. If you are prescribed light therapy, inform your doctor that you are using Protopic as it is not recommended to use Protopic and light therapy at the same time.
- If your doctor tells you to use Protopic twice weekly to keep your atopic dermatitis cleared, your condition should be reviewed by your doctor at least every 12 months, even if it remains under control. In children, maintenance treatment should be suspended after 12 months, to assess whether the need for continued treatment still exists.
- It is recommended to use Protopic ointment at the lowest possible strength, at the lowest frequency and for the shortest possible duration necessary. This decision should be based on your doctor's assessment of how your eczema responds to Protopic ointment.

Children
- Protopic 0.1 % ointment is **not approved for children younger than 16 years of age**. Therefore it should not be used in this age group. Please consult your doctor.
- The effect of treatment with Protopic on the developing immune system in children, especially the young, has not been established.

Other medicines, cosmetics and Protopic
Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines.

You may use moisturising creams and lotions during treatment with Protopic but these products should not be used within two hours of applying Protopic.

The use of Protopic at the same time as other preparations to be used on the skin or while taking oral corticosteroids (e.g. cortisone) or medicines which affect the immune system has not been studied.

Protopic with alcohol
While using Protopic, drinking alcohol may cause the skin or face to become flushed or red and feel hot.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Protopic contains butylhydroxytoluene (E321)
Protopic contains butylhydroxytoluene (E321), which may cause local skin reactions (e.g. contact dermatitis), or irritation to the eyes and mucous membranes.

3. How to use Protopic

Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

- Apply Protopic as a thin layer to affected areas of your skin.

- Protopic may be used on most parts of the body, including the face and neck and in the creases of your elbows and knees.
- Avoid using the ointment inside your nose or mouth or in your eyes. If the ointment gets on any of these areas, it should be thoroughly wiped off and/or rinsed off with water.
- Do not cover the skin being treated with bandages or wraps.
- Wash your hands after applying Protopic unless your hands are also being treated.
- Before applying Protopic after a bath or shower, be sure your skin is completely dry.

Adults (16 years of age and older)
Two strengths of Protopic (Protopic 0.03% and Protopic 0.1% ointment) are available for adult patients (16 years of age and older). Your doctor will decide which strength is best for you.

Usually, treatment is started with Protopic 0.1% ointment twice a day, once in the morning and once in the evening, until the eczema has cleared. Depending on the response of your eczema your doctor will decide if the frequency of application can be reduced or the lower strength, Protopic 0.03% ointment, can be used.

Treat each affected region of your skin until the eczema has gone away. Improvement is usually seen within one week. If you do not see any improvement after two weeks, see your doctor about other possible treatments.

You may be told by your doctor to use Protopic 0.1% ointment twice weekly once your atopic dermatitis has cleared or almost cleared. Protopic 0.1 % ointment should be applied once a day twice weekly (e.g. Monday and Thursday) to areas of your body commonly affected by atopic dermatitis. There should be 2–3 days without Protopic treatment between applications.
If symptoms reappear you should use Protopic twice daily as outlined above and arrange to see your doctor to review your treatment.

If you accidentally swallow some ointment
If you accidentally swallow the ointment, consult your doctor or pharmacist as soon as possible. Do not try to induce vomiting.

If you forget to use Protopic
If you forget to apply the ointment at the scheduled time, do it as soon as you remember and then continue as before.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Very common (may affect more than 1 in 10 people):
- burning sensation and itching

These symptoms are usually mild to moderate and generally go away within one week of using Protopic.

Common (may affect up to 1 in 10 people):
- redness
- feeling of warmth
- pain
- increased skin sensitivity (especially to hot and cold)
- skin tingling
- rash

- local skin infection regardless of specific cause including but not limited to: inflamed or infected hair follicles, cold sores, generalised herpes simplex infections
- facial flushing or skin irritation after drinking alcohol is also common

Uncommon (may affect fewer than 1 in 100 people):
- acne

Following twice-weekly treatment application site infections have been reported in adults.
Rosacea (facial redness), rosacea-like dermatitis, lentigo (presence of flat brown spots on the skin), oedema at the application site and herpes eye infections have been reported during post-marketing experience.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Protopic

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the tube and carton after EXP. The expiry date refers to the last day of that month.
Do not store above 25ºC.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Protopic contains
- The active substance is tacrolimus monohydrate.
  One gram of Protopic 0.1% ointment contains 1.0 mg tacrolimus (as tacrolimus monohydrate).
- The other ingredients are white soft paraffin, liquid paraffin, propylene carbonate, white beeswax, hard paraffin, butylhydroxytoluene (E321) and all-*rac*-α-tocopherol.

What Protopic looks like and contents of the pack
Protopic is a white to slightly yellowish ointment. It is supplied in tubes containing 10, 30 or 60 grams of ointment. Not all pack sizes may be marketed. Protopic is available in two strengths (Protopic 0.03% and Protopic 0.1% ointment).

Marketing Authorisation Holder
LEO Pharma A/S
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2750 Ballerup
Denmark

Manufacturer
Astellas Ireland Co. Ltd.
Killorglin
County Kerry
Ireland

LEO Laboratories Ltd.

285 Cashel Road
Crumlin, Dublin 12
Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

ANNEX IV

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS OF THE MARKETING AUTHORISATION(S)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for tacrolimus (topical formulations), the scientific conclusions of PRAC are as follows:

In view of available data on the risk of significant systemic absorption when used off-label to treat pyoderma gangrenosum from cases in the literature, the PRAC concluded that the product information of products containing topical tacrolimus should be amended to add pyoderma gangrenosum to the list of conditions mentioned in the SmPC for which tacrolimus ointment is not recommended.

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for tacrolimus (topical formulations) the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing tacrolimus (topical formulations) is unchanged subject to the proposed changes to the product information.

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.