ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Protopy 0.03% ointment

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For a 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

Treatment of moderate to severe atopic dermatitis in adults who are not adequately responsive to or are intolerant of conventional therapies such as topical corticosteroids. Treatment of moderate to severe atopic dermatitis in children (2 years of age and above) who failed to respond adequately to conventional therapies such as topical corticosteroids.

4.2 Posology and method of administration

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

Treatment should be intermittent and not continuous.

Protopy ointment should be applied as a thin layer to affected areas of the skin. Protopy ointment may be used on any part of the body, including face, neck and flexure areas, except on mucous membranes. Protopy ointment should not be applied under occlusion (see section 4.4).

Each affected region of the skin should be treated with Protopy until clearance occurs and then treatment should be discontinued. 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. Protopy can be used for short term and intermittent long term treatment. At the first signs of recurrence (flares) of the disease symptoms, treatment should be re-initiated.

Protopy is not recommended for use in children below age of 2 years until further data are available.

Use in children (2 years of age and above)
Treatment should be started twice a day for up to three weeks. Afterwards the frequency of application should be reduced to once a day until clearance of the lesion (see section 4.4).

Use in adults (16 years of age and above)
Protopy is available in two strengths, Protopy 0.03% and Protopy 0.1% ointment. Treatment should be started with Protopy 0.1% twice a day and treatment should be continued until clearance of the lesion. If symptoms recur, twice daily treatment with Protopy 0.1% should be restarted. An attempt should be made to reduce the frequency of application or to use the lower strength Protopy 0.03% ointment if the clinical condition allows.

Use in elderly (65 years of age and above)
Specific studies have not been conducted in elderly patients. However, the clinical experience available in this patient population has not shown the necessity for any dosage adjustment.

As clinical efficacy studies were performed with abrupt cessation of treatment, no information is available on whether tapering of the dosage would reduce recurrence rate.

4.3 Contraindications

Hypersensitivity to macrolides in general, to tacrolimus or to any of the excipients.

4.4 Special warnings and precautions for use

Protopy should not be used in patients with congenital or acquired immunodeficiencies or in patients on therapy that cause immunosuppression.

The effect of treatment with Protopy ointment on the developing immune system of children, especially the young, has not yet been established and this should be taken into account when prescribing to this age group (see section 4.1).

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 Protopy 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. Protopy ointment should not be applied to lesions that are considered to be potentially malignant or pre-malignant.

Emollients should not be applied to the same area within 2 hours of applying Protopy ointment. Concomitant use of other topical preparations has not been assessed. There is no experience with concomitant use of systemic steroids or immunosuppressive agents.

Protopy ointment has not been evaluated for its efficacy and safety in the treatment of clinically infected atopic dermatitis. Before commencing treatment with Protopy ointment, clinical infections at treatment sites should be cleared. Patients with atopic dermatitis are predisposed to superficial skin infections. Treatment with Protopy may be associated with an increased risk of herpes viral infections (herpes simplex dermatitis [eczema herpeticum], herpes simplex [cold sores], Kaposi's varicelliform eruption). In the presence of these infections, the balance of risks and benefits associated with Protopy use should be evaluated.
The potential for local immunosuppression (possibly resulting in infections or cutaneous malignancies) in the long term (i.e. over a period of years) is unknown (see section 5.1).

Protopy 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. In patients using tacrolimus ointment, cases of malignancies, including cutaneous and other types of lymphoma, and skin cancers have been reported (see section 4.8). Patients with atopic dermatitis treated with Protopy have not been found to have significant systemic tacrolimus levels.

Lymphadenopathy was uncommonly (0.8%) reported in clinical trials. The majority of these cases related to infections (skin, respiratory tract, tooth) and resolved with appropriate antibiotic therapy. Transplant patients receiving immunosuppressive regimens (e.g. systemic tacrolimus) are at increased risk for developing lymphoma; therefore patients who receive Protopy and who develop lymphadenopathy should be monitored to ensure that the lymphadenopathy resolves.
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 Protopy should be considered.

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

The use of Protopy ointment in patients with genetic epidermal barrier defects such as Netherton's syndrome is not recommended due to the potential for permanently increased systemic absorption of tacrolimus. The safety of Protopy ointment has not been established in patients with generalised erythroderma.

Care should be exercised if applying Protopy to patients with extensive skin involvement over an extended period of time, especially in children (see section 4.2).

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.

A potential interaction between vaccination and application of Protopy ointment has not been investigated. Because of the potential risk of vaccination failure, vaccination should be administered prior to commencement of treatment, or during a treatment-free interval with a period of 14 days between the last application of Protopy and the vaccination. In case of live attenuated vaccination, this period should be extended to 28 days or the use of alternative vaccines should be considered.

4.6 Pregnancy and lactation

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.

Protopy ointment should not be used during pregnancy unless clearly necessary.

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

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Protopy ointment is administered topically and is unlikely to have an effect on the ability to drive or 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, < 1/10) and uncommon (> 1/1,000, < 1/100). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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

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

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

Nervous system disorders
Common: Paraesthesias and dysaesthesias (hyperaesthesia, burning sensation)

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

The following adverse reactions have been reported during post-marketing experience:
Skin and subcutaneous tissue disorders: Rosacea

Post-marketing: cases of malignancies, including cutaneous and other types of lymphoma, and skin cancers, have been reported in patients using tacrolimus ointment (see section 4.4).

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: Other dermatologicals, ATC code: D11AX14

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.

Results from clinical studies in patients
The efficacy and safety of Protopy was assessed in more than 13,500 patients treated with tacrolimus ointment in Phase I to Phase III clinical trials. Data from four 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.

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.
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 Protopy 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.

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

Elimination
When administered intravenously, tacrolimus has been shown to have a low clearance rate. The average total body clearance is approximately 2.25 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.

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. 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

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

7. MARKETING AUTHORISATION HOLDER

Astellas Pharma GmbH
Neumarkter Str. 61
D-81673 München
Germany

8. MARKETING AUTHORISATION NUMBERS

EU/1/02/202/001
EU/1/02/202/002
EU/1/02/202/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28/02/2002
Date of renewal: 20/11/2006

10. DATE OF REVISION OF THE TEXT

{DD/MM/YYYY}

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

1. NAME OF THE MEDICINAL PRODUCT

Protopy 0.1% ointment

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 g of Protopy 0.1% ointment contains 1.0 mg of tacrolimus as tacrolimus monohydrate (0.1%).

For a 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

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.

4.2 Posology and method of administration

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

Treatment should be intermittent and not continuous.

Protopy ointment should be applied as a thin layer to affected areas of the skin. Protopy ointment may be used on any part of the body, including face, neck and flexure areas, except on mucous membranes. Protopy ointment should not be applied under occlusion (see section 4.4).

Each affected region of the skin should be treated with Protopy until clearance occurs and then treatment should be discontinued. 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. Protopy can be used for short term and intermittent long term treatment. At the first signs of recurrence (flares) of the disease symptoms, treatment should be reinitiated.

Protopy is not recommended for use in children below age of 2 years until further data are available.

Use in adults (16 years of age and above)
Protopy is available in two strengths, Protopy 0.03% and Protopy 0.1% ointment. Treatment should be started with Protopy 0.1% twice a day and treatment should be continued until clearance of the lesion. If symptoms recur, twice daily treatment with Protopy 0.1% should be restarted. An attempt should be made to reduce the frequency of application or to use the lower strength Protopy 0.03% ointment if the clinical condition allows.

Use in elderly (65 years of age and above)
Specific studies have not been conducted in elderly patients. However, the clinical experience available in this patient population has not shown the necessity for any dosage adjustment.

As clinical efficacy studies were performed with abrupt cessation of treatment, no information is available on whether tapering of the dosage would reduce recurrence rate.

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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 Protopy 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. Protopy ointment should not be applied to lesions that are considered to be potentially malignant or pre-malignant.

Emollients should not be applied to the same area within 2 hours of applying Protopy ointment. Concomitant use of other topical preparations has not been assessed. There is no experience with concomitant use of systemic steroids or immunosuppressive agents.

Protopy ointment has not been evaluated for its efficacy and safety in the treatment of clinically infected atopic dermatitis. Before commencing treatment with Protopy ointment, clinical infections at treatment sites should be cleared. Patients with atopic dermatitis are predisposed to superficial skin infections. Treatment with Protopy may be associated with an increased risk of herpes viral infections (herpes simplex dermatitis [eczema herpeticum], herpes simplex [cold sores], Kaposi's varicelliform eruption). In the presence of these infections, the balance of risks and benefits associated with Protopy use should be evaluated.
The potential for local immunosuppression (possibly resulting in infections or cutaneous malignancies) in the long term (i.e. over a period of years) is unknown (see section 5.1).

Protopy 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. In patients using tacrolimus ointment, cases of malignancies, including cutaneous and other types of lymphoma, and skin cancers have been reported (see section 4.8). Patients with atopic dermatitis treated with Protopy have not been found to have significant systemic tacrolimus levels.

Lymphadenopathy was uncommonly (0.8%) reported in clinical trials. The majority of these cases related to infections (skin, respiratory tract, tooth) and resolved with appropriate antibiotic therapy. Transplant patients receiving immunosuppressive regimens (e.g. systemic tacrolimus) are at increased risk for developing lymphoma; therefore patients who receive Protopy and who develop lymphadenopathy should be monitored to ensure that the lymphadenopathy resolves.
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 Protopy should be considered.

Care should be taken to avoid contact with eyes and mucous membranes. If accidentally applied to these areas, the ointment should be thoroughly wiped off and/or rinsed off with water.
The use of Protopy ointment under occlusion has not been studied in patients. Occlusive dressings are not recommended.
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A potential interaction between vaccination and application of Protopy ointment has not been investigated. Because of the potential risk of vaccination failure, vaccination should be administered prior to commencement of treatment, or during a treatment-free interval with a period of 14 days between the last application of Protopy and the vaccination. In case of live attenuated vaccination, this period should be extended to 28 days or the use of alternative vaccines should be considered.

4.6 Pregnancy and lactation

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.

Protopy ointment should not be used during pregnancy unless clearly necessary.

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

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Protopy ointment is administered topically and is unlikely to have an effect on the ability to drive or 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, < 1/10) and uncommon (> 1/1,000, < 1/100). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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

Nervous system disorders
Common: Paraesthesias and dysaesthesias (hyperaesthesia, burning sensation)

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

The following adverse reactions have been reported during post-marketing experience:
Skin and subcutaneous tissue disorders: Rosacea

Post-marketing: cases of malignancies, including cutaneous and other types of lymphoma, and skin cancers, have been reported in patients using tacrolimus ointment (see section 4.4).

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: Other dermatologicals, ATC code: D11AX14

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.

Results from clinical studies in patients
The efficacy and safety of Protopy was assessed in more than 13,500 patients treated with tacrolimus ointment in Phase I to Phase III clinical trials. Data from four 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.

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.
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 Protopy 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.

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

Elimination
When administered intravenously, tacrolimus has been shown to have a low clearance rate. The average total body clearance is approximately 2.25 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.

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. 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

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

7. MARKETING AUTHORISATION HOLDER

Astellas Pharma GmbH
Neumarkter Str. 61
D-81673 München
Germany

8. MARKETING AUTHORISATION NUMBERS

EU/1/02/202/003
EU/1/02/202/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28/02/2002
Date of renewal: 20/11/2006

10. DATE OF REVISION OF THE TEXT

{DD/MM/YYYY}

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

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Astellas Ireland Co. Ltd.,
Killorglin,
Co. Kerry,
Ireland

B CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

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

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

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

1. NAME OF THE MEDICINAL PRODUCT

Protopy 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.

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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: {MM/YYYY}

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

Astellas Pharma GmbH
Neumarkter Str. 61
D-81673 München
Germany

12. MARKETING AUTHORISATION NUMBERS

EU/1/02/202/005 10 g
EU/1/02/202/001 30 g
EU/1/02/202/002 60 g

13. BATCH NUMBER

Lot: {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Protopy 0.03%

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PROTOPY 0.03% OINTMENT (10 g TUBE)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Protopy 0.03% Ointment
Tacrolimus monohydrate
Cutaneous use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP: {MM/YYYY}

4. BATCH NUMBER

Lot: {number}

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 g

6. OTHER

Keep out of the reach and sight of children.

Do not store above 25°C.

Astellas Pharma GmbH
Neumarkter Str. 61
D-81673 München
Germany

EU/1/02/202/005

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

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

1. NAME OF THE MEDICINAL PRODUCT

Protopy 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.

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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: {MM/YYYY}

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

Astellas Pharma GmbH
Neumarkter Str. 61
D-81673 München
Germany

12. MARKETING AUTHORISATION NUMBERS

EU/1/02/202/001 30 g
EU/1/02/202/002 60 g

13. BATCH NUMBER

Lot: {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

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

1. NAME OF THE MEDICINAL PRODUCT

Protopy 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.

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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: {MM/YYYY}

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

Astellas Pharma GmbH
Neumarkter Str. 61
D-81673 München
Germany

12. MARKETING AUTHORISATION NUMBERS

EU/1/02/202/006 10 g
EU/1/02/202/003 30 g
EU/1/02/202/004 60 g

13. BATCH NUMBER

Lot: {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Protopy 0.1%

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PROTOPY 0.1% OINTMENT (10 g TUBE)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Protopy 0.1% Ointment
Tacrolimus monohydrate
Cutaneous use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP: {MM/YYYY}

4. BATCH NUMBER

Lot: {number}

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 g

6. OTHER

Keep out of the reach and sight of children.

Do not store above 25°C.

Astellas Pharma GmbH
Neumarkter Str. 61
D-81673 München
Germany

EU/1/02/202/006

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

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

1. NAME OF THE MEDICINAL PRODUCT

Protopy 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.

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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: {MM/YYYY}

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

Astellas Pharma GmbH
Neumarkter Str. 61
D-81673 München
Germany

12. MARKETING AUTHORISATION NUMBERS

EU/1/02/202/003 30 g
EU/1/02/202/004 60 g

13. MANUFACTURER'S BATCH NUMBER

Lot: {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Protopy 0.03% Ointment
Tacrolimus monohydrate

Read all of this leaflet carefully before you start using this medicine.
- 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. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Protopy is and what it is used for
2. Before you use Protopy
3. How to use Protopy
4. Possible side effects
5. How to store Protopy
6. Further information

1. WHAT PROTOPY IS AND WHAT IT IS USED FOR

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

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

2. BEFORE YOU USE PROTOPY

Do not use Protopy
- If you are allergic (hypersensitive) to tacrolimus or any of the other ingredients of Protopy or to macrolide antibiotics (e.g. azithromycin, clarithromycin, erythromycin).

Take special care with Protopy
- Protopy 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 Protopy on the developing immune system in children, especially the young, has not been established.
- The safety of using Protopy for a long time is not known. A very small number of people who have used Protopy ointment have had malignancies (for example, skin or lymphoma). However, a link to Protopy ointment treatment has not been shown.
- If you have infected lesions. Do not apply the ointment to infected lesions.
- If you have liver failure. Talk to your doctor before using Protopy.
- Also speak to your doctor before using Protopy 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 or if you suffer from generalised erythroderma (inflammatory reddening and scaling of the entire skin). Talk to your doctor before using Protopy.

- You should inform your doctor if you have swollen lymph nodes at initiation of treatment. If your lymph nodes become swollen during treatment with Protopy, consult your doctor.
- Before receiving a vaccination tell your doctor that you are using Protopy. Vaccinations should not be given during treatment and for a certain time after treatment with Protopy. For live attenuated vaccinations (e.g. measles, mumps, rubella or oral polio) the waiting time is 28 days, for inactivated vaccines (e.g. tetanus, diphtheria, pertussis or influenza) 14 days.
- Avoid exposing the skin to long periods of sunlight or artificial sunlight such as tanning beds. If you spend time outdoors after applying Protopy, 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 Protopy as it is not recommended to use Protopy and light therapy at the same time.
- Avoid contact with the eyes or mucous membranes (inside of your nose or mouth).

Taking or using other medicines and cosmetics
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

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

The use of Protopy 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.

Before receiving a vaccination tell your doctor that you are using Protopy (see Section "Take special care with Protopy").

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

Pregnancy and breast-feeding
Don't use Protopy if you are pregnant or breast-feeding.
Ask your doctor or pharmacist for advice before taking any medicine.

3. HOW TO USE PROTOPY

Always use Protopy exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

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

Protopy 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 Protopy unless your hands are also being treated.

Before applying Protopy after a bath or shower, be sure your skin is completely dry.

Children (2 years of age and older)
Apply Protopy 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 Protopy (Protopy 0.03% and Protopy 0.1% ointment) are available for adult patients. Your doctor will decide which strength is best for you. Usually, treatment is started with Protopy 0.1% ointment twice a day, once in the morning and once in the evening, until the eczema has cleared. If symptoms reappear, treatment with Protopy 0.1% twice a day should be restarted. Depending on the response of your eczema your doctor will decide if the frequency of application can be reduced or the lower strength, Protopy 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. Treatment with Protopy may be repeated if symptoms reappear.

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 Protopy
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 product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

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

Approximately half of the patients who use Protopy have some type of skin irritation where they have applied the ointment. Burning sensation and itching are very common (> 10%). These symptoms are usually mild to moderate and generally go away within one week of using Protopy. Other common (> 1%) side effects are redness, feeling of warmth, pain, increased skin sensitivity (especially to hot and cold), skin tingling, rash, folliculitis (inflamed or infected hair follicles) and herpes viral infections (e.g. cold sores, generalised herpes simplex infections). Facial flushing or skin irritation after drinking alcohol is also common. Acne is an uncommon side effect. Rosacea and rosacea-like dermatitis have also been reported.
Since commercial availability a very small number of people who have used Protopy ointment have had malignancies (for example, skin or lymphoma). However, a link to Protopy ointment treatment has not been confirmed or refuted on the available evidence so far.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE PROTOPY

Keep out of the reach and sight of children.

Do not use Protopy 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.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Protopy contains
- The active substance is tacrolimus monohydrate.
  One gram of Protopy 0.03% ointment contains 0.3 mg tacrolimus (as tacrolimus monohydrate).
- The other ingredients are white soft paraffin, liquid paraffin, propylene carbonate, white beeswax and hard paraffin.

What Protopy looks like and contents of the pack
Protopy 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. Protopy is available in two strengths (Protopy 0.03% and Protopy 0.1% ointment).

Marketing Authorisation Holder: Astellas Pharma GmbH, Neumarkter Str. 61, D-81673 München, Germany.

Manufacturer: Astellas Ireland Co. Ltd., Killorglin, County Kerry, Ireland.

For any information about this medicinal product, 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 (EMEA) web site: http://www.emea.europa.eu

PACKAGE LEAFLET: INFORMATION FOR THE USER

Protopy 0.1% Ointment
Tacrolimus monohydrate

Read all of this leaflet carefully before you start using this medicine.
- 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. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Protopy is and what it is used for
2. Before you use Protopy
3. How to use Protopy
4. Possible side effects
5. How to store Protopy
6. Further information

1. WHAT PROTOPY IS AND WHAT IT IS USED FOR

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

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

2. BEFORE YOU USE PROTOPY

Do not use Protopy
- If you are allergic (hypersensitive) to tacrolimus or any of the other ingredients of Protopy or to macrolide antibiotics (e.g. azithromycin, clarithromycin, erythromycin).

Take special care with Protopy
- Protopy 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 safety of using Protopy for a long time is not known. A very small number of people who have used Protopy ointment have had malignancies (for example, skin or lymphoma). However, a link to Protopy ointment treatment has not been shown.
- If you have infected lesions. Do not apply the ointment to infected lesions.
- Also speak to your doctor before using Protopy if you have any skin malignancies (tumours) or if you have a weakened immune system (immuno-compromised) whatever the cause.
- If you have liver failure. Talk to your doctor before using Protopy.
- If you have an inherited skin barrier disease such as Netherton's syndrome or if you suffer from generalised erythroderma (inflammatory reddening and scaling of the entire skin). Talk to your doctor before using Protopy.
- You should inform your doctor if you have swollen lymph nodes at initiation of treatment. If your lymph nodes become swollen during treatment with Protopy, consult your doctor.
- Before receiving a vaccination tell your doctor that you are using Protopy. Vaccinations should not be given during treatment and for a certain time after treatment with Protopy. For live

attenuated vaccinations (e.g. measles, mumps, rubella or oral polio) the waiting time is 28 days, for inactivated vaccines (e.g. tetanus, diphtheria, pertussis or influenza) 14 days.
- Avoid exposing the skin to long periods of sunlight or artificial sunlight such as tanning beds. If you spend time outdoors after applying Protopy, 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 Protopy as it is not recommended to use Protopy and light therapy at the same time.
- Avoid contact with the eyes or mucous membranes (inside of your nose or mouth).

Taking or using other medicines and cosmetics
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

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

The use of Protopy 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.

Before receiving a vaccination tell your doctor that you are using Protopy (see Section "Take special care with Protopy").

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

Pregnancy and breast-feeding
Don't use Protopy if you are pregnant or breast-feeding.
Ask your doctor or pharmacist for advice before taking any medicine.

3. HOW TO USE PROTOPY

Always use Protopy exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

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

Protopy 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 Protopy unless your hands are also being treated.

Before applying Protopy after a bath or shower, be sure your skin is completely dry.

Two strengths of Protopy (Protopy 0.03% and Protopy 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 Protopy 0.1% ointment twice a day, once in the morning and once in the evening, until the eczema has cleared. If symptoms reappear, treatment with Protopy 0.1% twice a day should be restarted. Depending on the response of your eczema your doctor will decide if the frequency of application can be reduced or the lower strength, Protopy 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. Treatment with Protopy may be repeated if symptoms reappear.

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 Protopy
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 product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

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

Approximately half of the patients who use Protopy have some type of skin irritation where they have applied the ointment. Burning sensation and itching are very common (> 10%). These symptoms are usually mild to moderate and generally go away within one week of using Protopy. Other common (> 1%) side effects are redness, feeling of warmth, pain, increased skin sensitivity (especially to hot and cold), skin tingling, rash, folliculitis (inflamed or infected hair follicles) and herpes viral infections (e.g. cold sores, generalised herpes simplex infections). Facial flushing or skin irritation after drinking alcohol is also common. Acne is an uncommon side effect. Rosacea and rosacea-like dermatitis have also been reported.
Since commercial availability a very small number of people who have used Protopy ointment have had malignancies (for example, skin or lymphoma). However, a link to Protopy ointment treatment has not been confirmed or refuted on the available evidence so far.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE PROTOPY

Keep out of the reach and sight of children.

Do not use Protopy 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.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Protopy contains
- The active substance is tacrolimus monohydrate.
  One gram of Protopy 0.1% ointment contains 1.0 mg tacrolimus (as tacrolimus monohydrate).
- The other ingredients are white soft paraffin, liquid paraffin, propylene carbonate, white beeswax and hard paraffin.

What Protopy looks like and contents of the pack
Protopy 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. Protopy is available in two strengths (Protopy 0.03% and Protopy 0.1% ointment).

Marketing Authorisation Holder: Astellas Pharma GmbH, Neumarkter Str. 61, D-81673 München, Germany.

Manufacturer: Astellas Ireland Co. Ltd., Killorglin, County Kerry, Ireland.

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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