SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Tacrolimus Accord 0.03% ointment

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram contains 0.3 mg of tacrolimus, as monohydrate.

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

Tacrolimus 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 **and adolescents** 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

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

Tacrolimus is available in two strengths, tacrolimus 0.03% ointment and tacrolimus 0.1% ointment.

Posology

Flare treatment

Tacrolimus can be used for short-term and intermittent long-term treatment. Treatment should not be continuous on a long-term basis.

Tacrolimus treatment should begin at the first appearance of signs and symptoms. Each affected region of the skin should be treated with tacrolimus 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 Tacrolimus 0.1% twice a day and treatment should be continued until clearance of the lesion. If symptoms recur, twice daily treatment with Tacrolimus 0.1% should be restarted. An attempt should be made to reduce the frequency of application or to use the lower strength Tacrolimus 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 Tacrolimus 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).

Tacrolimus 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 **and adolescents** (16 years of age and above) should use Tacrolimus 0.1% ointment.

Tacrolimus 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 tacrolimus 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 Tacrolimus 0.03% ointment.

Tacrolimus 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 tacrolimus 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.

Tacrolimus ointment should not be used in children aged below 2 years until further data are available.

Method of administration

Tacrolimus ointment should be applied as a thin layer to affected or commonly affected areas of the skin. Tacrolimus ointment may be used on any part of the body,

including face, neck and flexure areas, except on mucous membranes. Tacrolimus ointment should not be applied under occlusion because this method of administration has not been studied in patients (see section 4.4).

Patients should be advised not to bathe, shower or swim immediately after applying the ointment; water may wash off the medicine.

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 tacrolimus (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. Tacrolimus 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. Tacrolimus 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 tacrolimus 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 tacrolimus with respect to the response to treatment and the continuing need for treatment. After 12 months this evaluation should include suspension of tacrolimus treatment in paediatric patients (see section 4.2). The effect of treatment with tacrolimus ointment on the developing immune system of children aged below 2 years has not been established (see section 4.1).

Tacrolimus ointment 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 tacrolimus 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 tacrolimus 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 tacrolimus 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. Tacrolimus ointment has not been evaluated for its efficacy and safety in the treatment of clinically infected atopic dermatitis. Before commencing treatment with Tacrolimus ointment, clinical infections at treatment sites should be cleared. Treatment with tacrolimus 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 tacrolimus use should be evaluated.

Emollients should not be applied to the same area within 2 hours of applying Tacrolimus 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 Tacrolimus 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).

Instruct patients not to smoke or go near naked flames - risk of severe burns. Fabric (clothing, bedding, dressings etc.) that has been in contact with this product burns more easily and is a serious fire hazard. Washing clothing and bedding may reduce product build-up but not totally remove it.

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 meningitidis 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

Fertility

There are no fertility data available.

Pregnancy

There are no adequate data from the use of tacrolimus ointment in pregnant women. Studies in animals have shown reproductive toxicity following systemic administration (see section 5.3). The potential risk for humans is unknown.

Tacrolimus 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 Tacrolimus ointment is not recommended.

4.7 Effects on ability to drive and use machines

Tacrolimus ointment has no or negligible influence 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 to < 1/10) and uncommon (≥ 1/1,000 to < 1/100), Not known (cannot be estimated from the available data). 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		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		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 Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 tacrolimus 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 of the innovator 0.1% ointment compared to topical corticosteroid 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 multicenter, 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 of the innovator ointments compared to hydrocortisone acetate 1% ointment 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 multicenter, 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 of the innovator ointments compared to hydrocortisone acetate 1% ointment 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 multicenter 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) of the innovator ointment compared to vehicle

	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 tacrolimus 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 meningitidis 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.

Clinical efficacy and safety data of Tacrolimus 0.1% ointment

In a randomized, double-blind, placebo-controlled, three-arm, parallel assignment, multicenter, therapeutic equivalence trial, 650 adult patients with moderate to severe atopic dermatitis were included. Treatment duration was for up to 6 weeks. A total of 650 patients were to be randomised and dosed in ratio of 2:2:1 for the Tacrolimus 0.1% ointment, the innovator tacrolimus 0.1% ointment or placebo [vehicle (the ointment base)]. Patients were administered any one of the study products twice daily for 6 weeks at ratio of 2:2:1. The treatment arm was determined by the randomisation schedule. Patients visited the clinic on 9 different occasions for comparative safety and efficacy assessment.

Patients included in the per-protocol (PP) and intent-to-treat (ITT) populations were used for the evaluation of all primary and secondary endpoints. Out of 650 patients, 547 patients were qualified for PP set and 630 patients were qualified for ITT set. The primary endpoint was defined as mean % change from baseline (% CFB) in EASI total score for PP and ITT sets.

Table 5: Mean EASI score for PP set

Parameter	Tacrolimus 0.1% ointment (N=220)	The innovator 0.1% ointment (N=224)	Placebo (N=103)
Mean (SD) EASI total score at baseline	15.35 (12.150)	15.51 (11.486)	14.73 (12.203)
Mean (SD) EASI total score at end of treatment (week 6)	3.25 (4.899)	3.03 (4.962)	8.71 (10.593)
Absolute change from baseline to end of treatment in EASI total score	12.307 (10.2213)	12.525 (9.9890)	6.282 (5.9339)

Table 6: Mean EASI score for ITT set

Parameter	Tacrolimus 0.1% ointment (N=253)	The innovator 0.1% ointment (N=251)	Placebo (N=126)
Mean (SD) EASI total score at baseline	15.28 (11.835)	15.28 (11.356)	14.63 (11.501)
Mean (SD) EASI total score at end of treatment (week 6)	3.68 (5.968)	3.20 (5.461)	9.84 (11.863)
Absolute change from baseline to end of treatment in EASI total score	11.975 (9.9381)	12.012 (9.9221)	6.636 (6.7981)

Table 7: Efficacy of Tacrolimus 0.1% ointment vs the innovator 0.1% ointment at week 6

Parameters	Tacrolimus 0.1% ointment vs the innovator 0.1% ointment twice daily
Mean % CFB in EASI total score for PP set	-2.23% (95% CI: -8.60% to 4.13%) (N=547)

Mean % CFB in EASI total score of ITT set	-3.52% (95% CI: -11.01% to 3.97%) (N=630)

The 95% CI for the difference in mean % change of EASI total score from baseline for test versus innovator product for PP set lies within the pre-specified limit (-15.00%, 15.00%) for therapeutic equivalence.

Table 8: Efficacy of Tacrolimus 0.1% ointment and the innovator 0.1% ointment compared to placebo at week 6

Parameters	Tacrolimus 0.1% ointment twice daily	The innovator 0.1% ointment twice daily
Mean % CFB in EASI total score for PP set as compared to placebo	28.46% (97.5% CI: 19.62% to 37.30%) (N=547)	30.70% (97.5% CI: 21.88% to 39.51%) (N=547)
Mean % CFB in EASI total score for ITT set as compared to placebo	35.26% (97.5% CI: 25.12% to 45.41%) (N=630)	38.78% (97.5% CI: 28.62% to 48.95%) (N=630)

The lower limit of 97.5% CI for the difference in mean % change of EASI total score from baseline for Tacrolimus 0.1% ointment versus placebo and the innovator 0.1% ointment versus placebo is greater than 0 for PP set, which proves the superiority of Tacrolimus 0.1% ointment and the innovator 0.1% ointment compared to placebo.

The incidence and nature of most adverse events were similar in the two tacrolimus ointment treatment groups. The most frequently reported adverse events were application site pain, application site pruritus, pruritus, skin burning sensation, application site hypersensitivity, skin irritation, application site papules, application site warmth and dermatitis atopic. There were no clinically relevant changes in the laboratory values or vital signs in all treatment groups throughout the 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.

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 tacrolimus 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

Paraffin, white soft

Paraffin, liquid

Propylene carbonate

Beeswax, white

Paraffin, hard

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Unopened tube: 2 years
After first opening: 90 days

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Aluminum laminate tube with low-density-polyethylene inner coat 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

Accord Healthcare Limited

Sage House

319 Pinner Road

North Harrow

Middlesex

HA1 4HF

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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