COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Takrozem 1 mg/g ointment (tacrolimus monohydrate)

NL/H/4705/001/DC

Date: 6 March 2023

This module reflects the scientific discussion for the approval of Takrozem 1 mg/g ointment. The procedure was finalised in the United Kingdom (UK/H/5940/002/DC). After a transfer in 2018, the current RMS is the Netherlands. The report presented below reflects the original procedure at the time of finalisation in the UK and has not been changed or updated since.

Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

Decentralised Procedure

Tacrolimus Pierre Fabre 0.1 % ointment

(tacrolimus monohydrate)

Procedure No: UK/H/5940/002/DC

UK Licence No: PL 20693/0013

Pierre Fabre Dermatologie

LAY SUMMARY

Tacrolimus Pierre Fabre 0.1 % ointment (tacrolimus monohydrate)

This is a summary of the Public Assessment Report (PAR) for Tacrolimus Pierre Fabre 0.1 % ointment (PL 20693/0013; UK/H/5940/002/DC). For ease of reading, this product will be referred to as Tacrolimus Pierre Fabre in the remainder of this Lay Summary.

This summary explains how Tacrolimus Pierre Fabre was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

For practical information about using Tacrolimus Pierre Fabre, patients should read the package leaflet or contact their doctor or pharmacist.

What is Tacrolimus Pierre Fabre and what is it used for?
The application for Tacrolimus Pierre Fabre was submitted as a hybrid application, given that bioequivalence by means of plasma pharmacokinetic analysis cannot be established. The applicant has instead supplied a therapeutic equivalence study comparing the test and reference product. Assessment of the application concluded that the ointment is similar to a reference medicine containing the same active substance (tacrolimus) in the same dose, demonstrating therapeutic equivalence.

The reference medicine is Protopic 0.1% ointment (LEO Pharma A/S).

Tacrolimus Pierre Fabre is used to treat moderate to severe atopic dermatitis (eczema) in adults and adolescents who are not adequately responsive to or are intolerant of conventional therapies such as topical corticosteroids.

How does Tacrolimus Pierre Fabre work?
Tacrolimus Pierre Fabre contains the active ingredient tacrolimus monohydrate which is an immunomodulating agent. This works by altering the abnormal immune response and relieves the skin inflammation and the itch.

How is Tacrolimus Pierre Fabre used?
The pharmaceutical form of this medicine is an ointment. Usually a thin layer of Tacrolimus Pierre Fabre is applied to the affected areas of the skin.

Adults and adolescents (16 years of age and older)
The reference medicine, Protopic, is available in two strengths (Tacrolimus 0.03% and 0.1% ointment), whereas Tacrolimus 0.1% Pierre Fabre ointment is available in one strength. A doctor will decide which strength is best for the patient.

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

Patients should treat each affected region of the skin until the eczema has gone away. Improvement is usually seen within one week. If a patient does not see any improvement after two weeks, he/she should see a doctor about other possible treatments.

This medicinal product can only be obtained with a prescription from a doctor.

For further information on how Tacrolimus Pierre Fabre is used, please see the Summary of Product Characteristics or the package leaflet available on the MHRA website.

What benefits of Tacrolimus Pierre Fabre have been shown in studies?
Because Tacrolimus Pierre Fabre is considered to be therapeutically equivalent, to the reference product Protopic 0.1% ointment (LEO Pharma A/S), its benefits and risks are taken as being the same as those of the reference medicine.

What are the possible side effects of Tacrolimus Pierre Fabre?
Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most common side effects with Tacrolimus Pierre Fabre (which may affect more than 1 in 10 people) are burning sensation and itching. These symptoms are usually mild to moderate and generally go away within one week of using Tacrolimus Pierre Fabre.

The common side effects with Tacrolimus Pierre Fabre (which may affect up to 1 in 10 people) are redness, feeling of warmth, pain, increased skin sensitivity (especially to hot and cold), skin tingling and irritation, rash, local skin infection regardless of specific cause including but not limited to: inflamed or infected hair follicles, cold sores, generalised herps simplex infections, facial flushing or skin irritation after drinking alcohol is also common and application site hypersensitivity.

For the full list of restrictions, see the package leaflet.

For the full list of all side effects reported with Tacrolimus Pierre Fabre, see section 4 of the package leaflet available on the MHRA website.

Why was Tacrolimus Pierre Fabre approved?
The MHRA decided that Tacrolimus Pierre Fabre's benefits are greater than its risks and recommended that it be approved for use.

What measures are being taken to ensure the safe and effective use of Tacrolimus Pierre Fabre?
A risk management plan (RMP) has been developed to ensure that Tacrolimus Pierre Fabre is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Tacrolimus Pierre Fabre including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

Other information about Tacrolimus Pierre Fabre
Austria, Belgium, Denmark, Finland, France, Germany, Greece, Italy, Luxemburg, Norway, Portugal, Spain, Sweden, The Netherlands and the UK agreed to grant a Marketing Authorisation for Tacrolimus Pierre Fabre on 25 October 2017. A Marketing Authorisation was granted in the UK on 16 November 2017.

The full PAR for Tacrolimus Pierre Fabre follows this summary.

This summary was last updated in January 2018.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy the Member States considered that the application for Tacrolimus Pierre Fabre 0.1 % ointment (PL 20693/0013; UK/H/5940/002/DC), is approvable.

The product is a prescription-only medicine (POM) and is indicated in adults and adolescents (16 years of age and above).

Flare treatment

Adults and adolescents (16 years of age and above)

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

Maintenance treatment

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

This application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Austria, Belgium, Denmark, Finland, France, Germany, Greece, Italy, Luxemburg, Norway, Portugal, Spain, Sweden and The Netherlands as Concerned Member States (CMS). The application was submitted under Article 10.3 of Directive 2001/83/EC, as amended, as a hybrid application. The reference medicinal product is Protopic 0.1% ointment, the Marketing Authorisation Holder for which is LEO Pharma A/S, first authorised in Europe under a Centralised procedure on 28 February 2002 (EU/1/02/201/001-006).

A hybrid application under Article 10(3) is a correct legal basis, given that bioequivalence by means of plasma pharmacokinetic analysis cannot be established. The Applicant has instead supplied a therapeutic equivalence study in patients with atopic dermatitis. This is consistent with the CHMP Note for Guidance on locally applied, locally acting products (CPMP/EWP/239/95/final). The Applicant has compared the test and reference products in parallel arms of the study and has also included a third, placebo arm (to which test and reference product should be superior). This is consistent with the ICH guideline on choice of control group in clinical trials (CPMP/ICH/364/96:ICH E10).

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.

The Chemistry Pharmacy and Standards Expert Advisory Group (CPS EAG) considered the initial submission for this marketing authorisation application in February 2015. Following consideration of the applicant's responses and further data that were submitted, the approval of the marketing authorisation was recommended.

No new non-clinical studies were conducted, which is acceptable given that this is a hybrid application cross-referring to a product that has been licensed for over 10 years.

To support the application, the Marketing Authorisation Holder (MAH) submitted a therapeutic equivalence study to compare the test product Tacrolimus Pierre Fabre 0.1% Ointment and the reference product Protopic® (Tacrolimus Monohydrate) 0.1% Ointment (LEO Pharma A/S) in adult patients with

moderate to severe atopic dermatitis. The study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice are in place for this product type at all sites responsible for the manufacture, assembly and batch release of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports issued by the inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those non-Community sites.

All Member States agreed to grant a Marketing Authorisation for the above product at the end of the procedure (Day 210 – 25 October 2017). After a subsequent national phase, the UK granted a Marketing Authorisation (PL 20693/0013) for this product on 16 November 2017.

II QUALITY ASPECTS

II.1 Introduction

This product is an ointment containing tacrolimus monohydrate corresponding to 1.0 mg tacrolimus in 1 g of ointment, as the active ingredient.

Other ingredients consist of the pharmaceutical white soft paraffin, liquid paraffin, propylene carbonate, white beeswax and hard paraffin. Appropriate justification for the inclusion of each excipient has been provided.

All excipients comply with their respective European Pharmacopoeia monographs with the exception of propylene carbonate which complies with the United States Pharmacopeia (USP).

None of the raw materials used in the manufacture of Tacrolimus Ointment are of animal origin except white beeswax. Excipient manufacturer certify that white beeswax is manufactured without the use of raw materials of mammalian origin.

The finished product is packed in aluminium laminate tube with low-density-polyethylene inner coat fitted with a white polypropylene screw cap. The pack sizes are 10 g, 30 g and 60 g.

Not all pack sizes may be marketed.

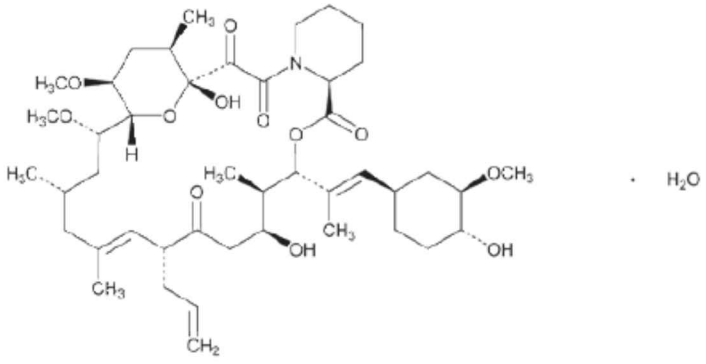
Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2. Drug Substance

INN: tacrolimus monohydrate

Chemical name:
[3S[3R*[E(1S*,3S*,4S*)],4S*,5R*,8S*,9E,12R*,14R*, 15S*,16R*,18S*,19S*,26aR*]]-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-15,19-epoxy-3H-pyrido [2,1-c][1,4] oxaazacyclotricosine -1,7,20,21 (4H,23H)- tetrone, monohydrate.

Structural formula:



Molecular formula: $C_{44}H_{69}NO_{12}H_2O$
Molecular mass: 822.03 g/mol
Appearance: White to off white powder.
Solubility: Soluble in methanol, ethanol, acetone, ethyl, acetate and chloroform. Insoluble in water.

Tacrolimus monohydrate is the subject of an active substance master file (ASMF).

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential impurities have been identified and monitored appropriately.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been provided supporting a suitable retest period when stored in the proposed packaging.

II.3. Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate a generic formulation of Tacrolimus Pierre Fabre ointment, which is robust, stable and is therapeutic equivalent to the reference product Protopic 0.1% ointment (LEO Pharma A/S).

A satisfactory account of the pharmaceutical development has been provided.

Comparative physico-chemical study, impurity profiles and therapeutic equivalence study have been provided for the proposed and originator products.

Manufacture of the product

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on commercial scale batches have been provided.

Finished Product Specification

The finished product specification proposed is acceptable. The test methods that have been described have been adequately validated. Batch data have been provided and all of the test and results comply with the release specifications.

Stability of the Product

Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. The data from these studies support a shelf life of 3 years for unopened tubes which reduces to 90 days once opened. The storage condition is ‘Store below 25°C’.

Therapeutic Equivalence
Bioequivalence studies are not necessary to support this application. For products for local application intended to act without systemic absorption, the approach to determine equivalence on systemic measurements is not applicable and pharmacodynamics or comparative clinical studies are required. The applicant has submitted one clinical study to establish therapeutic equivalence between the proposed product and the reference product. This study is discussed in Section IV.

The microstructure and rheology of the product have been considered adequately characterised and are routinely controlled at release and end of shelf life.

Further to the specified controls for microstructure and rheology of the drug product, the control strategy for the critical physical quality attributes of the drug product also includes appropriate material (excipients) attributes and applied critical process parameters in the manufacture of the drug product.

Therapeutic equivalence has been demonstrated with Tacrolimus Pierre Fabre 0.1% ointment versus Protopic 0.1% ointment. Furthermore, equivalent *in vitro* drug release performance, using synthetic membranes, has been established between the test and reference products.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The applicant has provided a post-approval commitment to review specification limits based on statistical analysis of available batch analysis and stability data including further commercial scale batches.

There are no objections to the approval of this application from a pharmaceutical point of view.

III NON-CLINICAL ASPECTS

III.1 Introduction

The pharmacodynamic, pharmacokinetic and toxicological properties of tacrolimus are well-known. As this is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. An overview based on literature review is, thus, appropriate.

The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

Histopathological findings, which were deemed to be indicative of immunosuppression, were observed in the thymus, lymph nodes, bone marrow, lungs, stomach and rectum. Exposures to a known impurity is higher than the expected maximum human exposure. The known impurity has been sufficiently qualified from a toxicological perspective.

Tacrolimus was negative in the Bacterial Reverse mutation and Chromosome aberration tests.

The potential clinical exposure will be low and therefore renal findings seen at the no-observed-adverse-effect-level (NOAEL) in the 28 day rat study are unlikely to be of clinical significance.

III.2 Pharmacology

Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.3 Pharmacokinetics

Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.4 Toxicology
Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Since this product is intended for substitution of an originator product, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects
There are no objections to the approval of this application from a non-clinical point of view.

IV CLINICAL ASPECTS
IV.1 Introduction
The clinical pharmacology of tacrolimus is well-known. With the exception of the clinical study detailed below, no new pharmacodynamics or pharmacokinetic data are provided or required for this application.

IV.2 Pharmacokinetics
The clinical overview provides adequate background information on pharmacokinetics of tacrolimus.

IV.3 Pharmacodynamics
The clinical overview provides background information on pharmacodynamics of tacrolimus.

IV.4 Clinical efficacy
In support of this application, the applicant has submitted the following therapeutic equivalence study.

In accordance with the CHMP Note for Guidance on locally applied, locally acting products (CPMP/EWP/239/95/final) the applicant has submitted a clinical study of therapeutic equivalence in adult patients with atopic dermatitis.

A randomised, double blind, placebo-controlled, three-arm, parallel assignment, multi-centre, therapeutic equivalence study of the test product, Tacrolimus Pierre Fabre Ointment 0.1%, and the reference product, Protopic® (Tacrolimus Monohydrate) Ointment 0.1% (LEO Pharma A/S) in adult patients with moderate to severe atopic dermatitis.

The study was a randomised, double blind, placebo-controlled, three-arm, six-week active treatment, parallel assignment, therapeutic equivalence study in patients with moderate to severe Atopic Dermatitis [(i.e. a score of at least 4.5) as defined by the scoring system of Rajka and Langeland]. As per protocol, a total of 650 patients were to be randomised and dosed in ratio of 2:2:1 for the test product, reference product or placebo (comparator).

The overall study design was considered acceptable.

The study was carried out in compliance with the protocol, in adherence to Good Clinical Practice and other applicable regulatory requirements.

Study objectives:
The stated primary objective of the study was to establish therapeutic equivalence between Tacrolimus Pierre Fabre ointment 0.1% the test product and Protopic (tacrolimus) ointment 0.1%, the reference listed product manufactured by LEO Pharma A/S, and to show superiority over vehicle in the treatment of moderate to severe atopic dermatitis in the adult population.

The secondary objectives were to compare the adverse event profiles of the two ointments and to investigate their systemic absorption at anticipated C_{max}.

650 patients were planned to be enrolled.

Investigational Medicinal Product [test product, reference product or Placebo (Comparator)] was applied as a thin layer (1 cm ribbon spread over approx. 100 cm^2 affected skin surface) gently using finger(s) to all affected areas twice daily for up to 6 weeks. Additional 1 week application was continued if all the baseline lesions were found to have completely cleared by the Investigator on the scheduled visit prior to 6 weeks so as to ensure minimum 3 weeks active treatment of study drugs. Hence, ointment application was continued for a minimum of 3 weeks regardless of clearance of lesions. Study medications were dispensed at visit 2 (week 0), visit 4 (week 1), visit 5 (week 2), Visit 6 (Week 3) and Visit 7 (Week 4).

Patients were instructed to continue the treatment for the entire 6-week period unless all lesions had cleared as confirmed by the investigator on the immediate next scheduled / unscheduled visit while ensuring minimum 3 week application of the investigational products regardless of clearance of lesions. Patients were instructed to not to use the ointment on any mucous membranes, to avoid bathing after application, to avoid exposure to sunlight and not to apply emollients or other topical medications to the same areas of tacrolimus application. Patients were also instructed not to apply the ointment on lesions considered potentially malignant or pre-malignant.

Primary efficacy endpoint:
Mean percentage change from baseline in the Eczema Area and Severity Index (EASI) score at Week 6 / End of Treatment (EOT) visit.

Secondary efficacy endpoints:

1. Percentage of patients with ≥ 60% improvement in EASI total score at Week 6 / End of Treatment (EOT) Visit.
2. Change in grading of AD as defined by the scoring system of Rajka and Langeland from baseline as measured at Week 6 / EOT visit.
3. Percentage of body surface area affected (BSA affected) at Week 6 / EOT visit
4. Physician's assessment of individual signs of atopic dermatitis at week 6 / EOT visit.
5. Patient's assessment of pruritus at week 6 / EOT visit.

The primary and secondary efficacy endpoints were considered acceptable.

Blood samples for pharmacokinetic evaluation were planned at Day 4 and Day 14 at anticipated C_{max} in a sub-group of patients to investigate the systemic absorption of the investigational product.

Medical history, demography, physical examination, and vital signs assessment, serum and urine pregnancy test, tests for hematology, blood/serum biochemistry, immunology and urine analysis and ECG recording were done as a part of safety evaluation. Patients were monitored for adverse events during the conduct of study.

Analysis Sets:
Patients included in the per protocol (PP) and intent-to-treat (ITT) populations were used for the evaluation of all primary and secondary endpoints.

• Primary Efficacy Analysis
Primary efficacy analysis was presented on Mean % change from baseline (%CFB) in EASI total score for PP and ITT population.

The analysis of covariance (ANCOVA) was performed on % CFB of EASI total score considering Visit 2 as covariate and 95% CI was calculated to prove therapeutic equivalence of test versus reference with alpha = 5%. A point estimate and a two-sided 95% confidence interval (CI) were reported for the difference in % CFB of EASI total score.

Therapeutic equivalence of test product with that of reference product was concluded, if 95% CI fell within ±15% equivalence limits, for PP population.
The Applicant draws on published clinical studies to support an equivalence margin of +/- 15%. Clinical relevance is also supported by the additional analyses of absolute change from baseline in EASI where the equivalence margin of +/- 6.6 was set by an acknowledged minimum clinically important difference (MCID) between treatment groups in change from baseline EASI.

ANCOVA was performed on % CFB of EASI total score considering Visit 2 as covariate and 97.5% CI was calculated to prove superiority of test and reference over placebo with alpha = 2.5%. A point estimate and a one-sided 95% (i.e. 97.5%) CI was reported for the difference in % CFB of EASI total score.
Superiority of the test product and the reference product over placebo was concluded if the lower limit of the one-sided 95% CI for the difference observed in % CFB of EASI total score between test and placebo and reference and placebo was greater than zero, for PP population.

Percentage change, as opposed to absolute change, from baseline was introduced as an amendment to the Statistical Analysis Plan but this was done prior to database lock and therefore considered in principle acceptable. Furthermore, percentage change from baseline would be more likely to reveal heterogeneity and therefore be more sensitive to revelation of inequivalence as asserted.

• **Secondary Efficacy Analysis**
Secondary efficacy analysis was evaluated for the PP and ITT population.

Safety:
The safety analysis was performed using the safety population. Safety variables included Adverse events (AEs), clinical laboratory parameters, vital signs, physical examinations. Safety variables were listed and summarized with descriptive statistics, as appropriate.

Changes in the Conduct of the Study or Planned Analysis
Percentage change from baseline instead of change from baseline in Eczema Area and Severity Index (EASI) total score at EOT were reported.
Percentage change from baseline was calculated and reported instead of change from baseline for all efficacy analysis.

Results
Patient disposition:
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.

A total of 86% (560/650) completed the study. Although the dropout rate of 14% is less than originally anticipated, the rate of completion varied substantially between centre from 36% to 100%. The proportion of patients who discontinue was higher in the placebo group and test group compared to the reference group. The most frequent reasons for discontinuation in the Test and Placebo groups are consent withdrawal and meeting withdrawal criteria. The most frequent reasons for withdrawal in the Reference group are lost to follow up and consent withdrawal.

Demographics

The mean age for the dosed 650 patients was 38.9 ± 14.34 years. The racial make-up of the study was 68.15% Asian, 17.08% White, 14.62% Caucasian and 0.15% Black.

Table 14.1.1
Demographic Data And Other Baseline Characteristics (Safety Set)

	Statistics	Test (N=262)	Reference (N=256)	Placebo (N=132)	Total (N=650)
Age (Years)					
	n	262	256	132	650
	Mean (SD)	39.2 (14.15)	39.2 (14.52)	37.8 (14.43)	38.9 (14.34)
	Median	37.0	37.0	36.0	37.0
	Min, Max	18, 70	18, 70	18, 69	18, 70
Sex					
Male	n (%)	135 (51.53%)	147 (57.42%)	76 (57.58%)	358 (55.08%)
Female	n (%)	127 (48.47%)	109 (42.58%)	56 (42.42%)	292 (44.92%)
Race					
Asian	n (%)	179 (68.32%)	176 (68.75%)	88 (66.67%)	443 (68.15%)
White	n (%)	48 (18.32%)	43 (16.80%)	20 (15.15%)	111 (17.08%)
Caucasian	n (%)	35 (13.36%)	36 (14.06%)	24 (18.18%)	95 (14.62%)
Black	n (%)	0 (0.00%)	1 (0.39%)	0 (0.00%)	1 (0.15%)
Ethnicity					
Hispanic	n (%)	2 (0.76%)	0 (0.00%)	0 (0.00%)	2 (0.31%)
Non Hispanic	n (%)	260 (99.24%)	256 (100.00%)	132 (100.00%)	648 (99.69%)

Primary efficacy analysis:

The point estimate and confidence interval for difference between test and reference in mean % change in EASI Total Score from baseline to end of treatment for PP and ITT set are summarised in the tables below:

Table 1: Point estimate and confidence interval for difference in mean % change of EASI score from baseline (PP set, N=547)

Comparison	Point Estimate (%)	CI	Obtained Range (%)	Acceptance Range (%)	Conclusion
Test vs. Reference	-2.23	95.0%	(-8.60, 4.13)	(-15.00, 15.00)	Therapeutic Equivalent
Test vs. Placebo	28.46	97.5%	(19.62, 37.30)	Lower Limit > 0	Superior
Reference vs. Placebo	30.70	97.5%	(21.88, 39.51)	Lower Limit > 0	Superior

The 95% confidence interval for the difference in mean percentage change in the EASI score between test and reference products for the Per Protocol population was -8.60 to +4.13% and therefore within the pre-specified equivalence margin (-15% to +15%).

A placebo arm was included for assay sensitivity. The lower limit of the 97.5% confidence interval for test versus placebo and reference versus placebo is greater than zero for the PP set. Therefore, both test and reference products are superior to placebo.

The lower limit of the confidence interval for the test versus placebo comparison (19.62%) and reference versus placebo comparison (21.88%) is higher than the specified upper bound for the acceptance limit of 15% for equivalence. This supports a conclusion that test and reference products are superior to placebo by a clinically meaningful amount.

Table 2: Point estimate and confidence interval for difference in mean % change of EASI score from baseline (ITT set, N=630)

Comparison	Point Estimate (%)	CI	Obtained Range (%)
Test vs. Reference	-3.52	95.0%	(-11.01, 3.97)
Test vs. Placebo	35.26	97.5%	(25.12, 45.41)
Reference vs. Placebo	38.78	97.5%	(28.62, 48.95)

The 95% confidence interval for the difference between Test and Reference products in mean % change in EASI score from baseline (-11.01, +3.97%) for the ITT population is within the pre-specified acceptance limits of (-15.00, +15.00%) for equivalence demonstration.

In the ITT population, the lower limit of the 97.5% confidence interval for test versus placebo and reference versus placebo is greater than zero for the PP set. Therefore, both test and reference product are superior to placebo.

In the ITT population, the lower limit of the confidence interval for the test versus placebo comparison (25.12%) and reference versus placebo comparison (28.62%) is higher than the specified upper bound for the acceptance limit of 15% for equivalence. This would support a conclusion that test and reference products are superior to placebo by a clinically meaningful amount.

The change from baseline and the percentage change from baseline were similar for test and reference products at all study visits and in all cases statistically superior to placebo.

Efficacy conclusion:
Since the 95% CI for the difference in mean % change of EASI Total Score from baseline for test versus reference product lies within the pre-specified limit for therapeutic equivalence, it can be concluded that test product (Tacrolimus Pierre Fabre ointment 0.1%) is therapeutically equivalent to reference product [Protopic® (Tacrolimus monohydrate) ointment 0.1%]. It can be concluded that the efficacy of the test product is neither inferior nor superior to the reference product by a clinically meaningful amount.

Since lower limit of 97.5% CI for the difference in mean % change of EASI Total Score from baseline for test versus placebo product and reference versus placebo is greater than 0, it can be concluded that both test product (Tacrolimus Pierre Fabre ointment 0.1%) and reference product [Protopic® (Tacrolimus monohydrate) ointment 0.1%] are superior to placebo [Vehicle (the ointment base)].

Safety analysis:
The patients were exposed to 6 week treatment (twice daily) of either the test product or the Reference product or Placebo (Comparator) as per the randomisation schedule in ratio of 2:2:1.

A total of one hundred eighty one (181) adverse events (AEs) were reported by 118 patients during the conduct of study.
Out of the total 181 adverse events, 86 adverse events were mild, 88 AEs were moderate and 07 AEs were severe.

IV.5 Clinical safety

The commonest side effects in approximately 50% of patients are related to skin irritation at the application site. Burning sensation, pruritus and erythema are all common local side-effects.

There is a recognized increased incidence of bacterial and viral skin infection – including the serious conditions of disseminated herpex simplex infection leading to eczema herpeticum or a similar condition of Kaposi's varicelliform eruption where the identity of the disseminated viral infection is unknown – in patients treated with topical tacrolimus. In section 4.4 of the SmPC it is made clear that clinical infections at treatment sites should be cleared before commencement of treatment with tacrolimus ointment.

Post-marketing data has also revealed cases of cutaneous malignancy including cutaneous lymphoma and other types of skin cancer in patients using Tacrolimus Pierre Fabre ointment.

Amendments have been implemented in section 4.4 of the SmPC to improve prescriber understanding of the risk of skin infection and malignancy arising from cutaneous immunosuppression, and measures to minimize this.

IV.6 Risk Management Plan (RMP)

The Marketing Authorisation Holder (MAH) has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Tacrolimus Pierre Fabre 0.1 % ointment.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risk: Application site pruritus/irritation/burning	Section 4.8 and 5.1 of proposed SPC and corresponding section of PIL has information on this safety concern. Other routine risk minimisation measure includes the status of the product as "prescription only".	Currently available data does not support the need for additional risk minimization activities.
Important identified risk: Paraesthesia	Section 4.8 of proposed SPC and corresponding section of PIL has information on this safety concern. Other routine risk minimisation measure includes the status of the product as "prescription only".	Currently available data does not support the need for additional risk minimization activities.
Important identified risk: Alcohol flushing	Section 4.8 and 5.1 of proposed SPC and corresponding section of PIL has information on this safety concern. Other routine risk minimisation measure includes the status of the product as "prescription only".	Currently available data does not support the need for additional risk minimization activities.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risk: Folliculitis/herpes simplex	Section 4.4 and 4.8 of proposed SPC and corresponding section of PIL has information on this safety concern. Other routine risk minimisation measure includes the status of the product as "prescription only".	Currently available data does not support the need for additional risk minimization activities.
Important identified risk: Systemic absorption in conjunction with extensive, inherited or acquired, defects of skin barrier function	Section 4.4 of proposed SPC and corresponding section of PIL has information on this safety concern. Other routine risk minimisation measure includes the status of the product as "prescription only".	Currently available data does not support the need for additional risk minimization activities.
Important potential risk: Risk of cutaneous malignancy including Cutaneous T-cell lymphoma	Section 4.4 and 4.8 of proposed SPC and corresponding section of PIL has information on this safety concern. Other routine risk minimisation measure includes the status of the product as "prescription only".	Currently available data does not support the need for additional risk minimization activities.
Important potential risk: Risk of other lymphoma	Section 4.4, 4.8 and 5.3 of proposed SPC and	Currently available data does not support the need for

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	corresponding section of PIL has information on this safety concern. Other routine risk minimisation measure includes the status of the product as "prescription only".	additional risk minimization activities.
Important potential risk: Off-label use of tacrolimus ointment 0.1% in children between 2-16 years of age	Section 4.2 and 4.4 of proposed SPC and corresponding section of PIL has information on this safety concern. Other routine risk minimisation measure includes the status of the product as "prescription only".	Currently available data does not support the need for additional risk minimization activities.
Missing information: Children below 2 years of age	Section 4.2 of proposed SPC and corresponding section of PIL has information on this safety concern. Other routine risk minimisation measure includes the status of the product as "prescription only".	Currently available data does not support the need for additional risk minimization activities.
Missing information: Safety of maintenance treatment beyond 12 months (children above 2 years of age)	Section 4.2 and 4.4 of proposed SPC and corresponding section	Currently available data does not support the need for additional risk minimization activities.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	of PIL has information on this safety concern. Other routine risk minimisation measure includes the status of the product as "prescription only".	

Routine pharmacovigilance and routine risk minimisation are proposed. No additional measures are proposed.

IV.7 Discussion on the clinical aspects

With the exception of the therapeutic equivalence study, no new clinical data were submitted and none are required for this type of application.

There are no objections to the approval of this application from a clinical viewpoint**.**

The grant of a Marketing Authorisation is recommended for this application.

V User consultation

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to a user test bridging report referring to two parent leaflets: the leaflet for Protopic ointment (Parent PIL-1) for key information on safe use and the leaflet for 'Zolendronic acid 4 mg/ml concentrate for solution for injection' (Parent PIL-2) for layout, font size and formating of the leaflet. The bridging report submitted by the applicant is acceptable.

VI Overall conclusion, benefit/risk assessment and recommendation

The quality of the product is acceptable, and no new non-clinical or clinical concerns have been identified. Extensive clinical experience with tacrolimus monohydrate is considered to have demonstrated the therapeutic value of the compound. The benefit risk assessment is, therefore, considered to be positive.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for Tacrolimus Pierre Fabre 0.1% ointment is presented below:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Tacrolimus Pierre Fabre 0.1 % Ointment (10 g, 30 g, 60 g CARTON)

1. NAME OF THE MEDICINAL PRODUCT

Tacrolimus Pierre Fabre 0.1 % ointment
tacrolimus

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Paraffin, white soft; paraffin liquid; propylene carbonate; beeswax, white; paraffin hard.

4. PHARMACEUTICAL FORM AND CONTENTS

Ointment

10 g
30 g
60 g

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Cutaneous use

Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: {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

Pierre Fabre Dermatologie
45 place Abel Gance
92100 Boulogne
FRANCE

12. MARKETING AUTHORISATION NUMBER(S)

PL 20693/0013

13. BATCH NUMBER

Lot: {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Tacrolimus Pierre Fabre 0.1%

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

<PC: {number}
SN: {number}
NN: {number}>

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Tacrolimus Pierre Fabre 0.1 % Ointment (10 g tube)

1. NAME OF THE MEDICINAL PRODUCT

Tacrolimus Pierre Fabre 0.1 % intment
tacrolimus
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

Ointment
10 g

6. OTHER

Keep out of the sight and reach of children.

Do not store above 25°C.

MA Holder
Pierre Fabre Dermatologie

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Tacrolimus Pierre Fabre 0.1 % Ointment (30 g, 60 g TUBE)

1. NAME OF THE MEDICINAL PRODUCT

Tacrolimus Pierre Fabre 0.1 % ointment
tacrolimus

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Paraffin, white soft; paraffin liquid; propylene carbonate; beeswax, white; paraffin hard.

4. PHARMACEUTICAL FORM AND CONTENTS

Ointment

30 g
60 g

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Cutaneous use

Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: {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

Pierre Fabre Dermatologie
45 place Abel Gance
92100 Boulogne
FRANCE

12. MARKETING AUTHORISATION NUMBER(S)

PL 20693/0013

13. BATCH NUMBER

Lot: {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. OTHER

Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached Y/N (version)