COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Tacrolimus Accord 1 mg/g, ointment

(tacrolimus monohydrate)

NL/H/4570/001/DC

Date: 1 February 2021

This module reflects the scientific discussion for the approval of Tacrolimus Accord 1 mg/g, ointment. The procedure was finalised on 25 October 2017 with the United Kingdom as RMS (UK/H/5921/002/DC). The current RMS is the Netherlands (NL/H/4570/001/DC). For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Tacrolimus Accord 1 mg/g, ointment, from Accord Healthcare B.V.

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).

A comprehensive description of the indications and posology is given in the SmPC.

This application was submitted using the Decentralised Procedure (DCP), with the United Kingdom as Reference Member State (RMS) Austria, Cyprus, Denmark, Finland, Germany, Malta, Norway, Sweden, The Republic of Ireland and The Netherlands as Concerned Member States (CMS). The role of RMS was transferred to the Netherlands on 12 February 2019.

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 Accord 0.1% Ointment 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 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.

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

The active substance is tacrolimus monohydrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Tacrolimus is a white to off white powder and soluble in methanol, ethanol, acetone, ethyl, acetate and chloroform and insoluble in water.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

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.

Quality control of drug substance

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.

Stability of drug substance

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

Manufacturing process

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.

Quality control of drug product

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 drug 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'.

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 Ecotoxicity/environmental risk assessment (ERA)

Since Tacrolimus Accord is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

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.

IV. CLINICAL ASPECTS

IV.1 Introduction

A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. 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 Clinical efficacy

In support of this application, the applicant has submitted a 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 Accord 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 anddosed 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 Accord 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 cm2 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),Visit6 (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 mITT 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 were 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 Accord 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 Accord 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 randomization schedule in ratio of2:2:1.

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.3 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 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.4 Risk Management Plan

The 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 Accord.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	- Application site pruritus/irritation/burning - Paraesthesia - Alcohol flushing - Folliculitis/herpes simplex - Systemic absorption in conjunction with extensive, inherited or acquired, defects of skin barrier function
Important potential risks	- Risk of other lymphoma - Off-label use of tacrolimus ointment 0.1% in children between 2-16 years of age
Missing information	- Children below 2 years of age - Safety of maintenance treatment beyond 12 months (children above 2 years of age)

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

IV.5 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 formatting 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.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse