LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Efrinter
(ivermectin)

SE/H/2399/01/DC

This module reflects the scientific discussion for the approval of Efrinter. The procedure was finalised at 2025-09-24. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have agreed to grant a marketing authorisation for Efrinter, 10 mg/g, Cream.

The active substance is ivermectin. A comprehensive description of the indication and posology is given in the SmPC.

II. EXECUTIVE SUMMARY

II.1 About the product

Efrinter Cream contains ivermectin 10 mg/g as the active drug substance. It is a generic product whose formulation was developed according to Soolantra 10 mg/g cream for the topical treatment of papulopustular of rosacea in adult patients. Ivermectin has anti-inflammatory and anti-parasitic action, inducing the death of Demodex mites that have been reported to be a factor in inflammation of the skin.

The applicant applies for the following indication: *Topical treatment of rosacea (papulopustular) in adults.*

Efrinter is not approved in any country or region worldwide.

II.2 General comments on the submitted dossier

The application for Efrinter, 10 mg/g, cream, is a hybrid application submitted according to Article 10(3) of Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and ES, IT, PT as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Soolantra 10 mg/g cream authorised in Malta since 2015, with GALDERMA INTERNATIONAL as marketing authorisation holder.

The reference product used in the bioequivalence study is Soolantra, 10 mg/g, cream, with Galderma Laboratorium as marketing authorisation holder.

II.3 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly 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, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

GMP active substance
Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturer(s) responsible for manufacture of the finished product and batch release situated in the EU.

GCP
No issues regarding GCP have been identified. The clinical facility was inspected by the ES authority in 2023 and the bioanalytical facility was inspected by the UK authority in 2021 and ES authority in 2023, without any critical findings.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance
The structure of the drug substance has been adequately proven, and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described, and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

Drug Product
The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III.2 Non-clinical aspects

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of ivermectin are well known. As ivermectin is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

The non-clinical overview has been written by Feryal Cabuk, M.D., PhD, Senior Medical Manager, Humanis Saglik A.S. Turkey, and is dated 23 March, 2023. The report refers 25 publications up to year 2021.

Environmental Risk Assessment (ERA)
Since Efrinter is a generic product based on a hybrid Application for a topical product, it will not lead

to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Efrinter 10mg/g cream from a non-clinical point of view.

III.3 Clinical aspects

Pharmacokinetics
Efrinter cream is not a simple formulation and demonstration of equivalence with respect to quality is not considered sufficient. According to Guideline on quality and equivalence of locally applied, locally acting cutaneous products (EMA/CHMP/QWP/708282/2018), additional permeation kinetic studies are required for more complex formulations.
An in vivo pharmacokinetic bioequivalence study has been submitted comparing the applied product Efrinter, 10 mg/g, cream with the reference product Soolantra 10 mg/g cream.

Pharmacokinetic properties of the active substance
The terminal half-life averaged 6 days (mean: 145 hours, range 92-238 hours) in patients receiving a once daily cutaneous application of the medicinal product for 28 days.

Study C1B01784
Methods
This was a two-treatment, four-period, two-sequence, fully-replicate, single-dose crossover study conducted in 44 healthy volunteers under fasting conditions. A single dose [1 g ± 0.030 g] of either test product Ivermectin 1% cream or reference product Soolantra 10 mg/g cream was applied as a thin layer across the entire face (avoiding the eyes, lips and mucosa) as per the randomization schedule of each subject at ambient temperature in each period under the supervision of trained study personnel. Blood samples for concentration analysis were collected pre-dose and up to 21 days post-dose. Plasma concentrations of ivermectin were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 6th March and 11th July 2024.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for ivermectin, n=43.

Treatment	AUC_{0-t} pg*h/ml	C_{max} pg/ml	t_{max} h
Test	47162 ± 36469	605.603 ± 434.929	24.0 (9.0-24.0)
Reference	49099 ± 33495	629.442 ± 450.257	24.0 (12.0-48.2)
***Ratio (90% CI)**	100.81 (92.06-110.40)	101.42 (92.17-111.61)	-
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum plasma concentration			

**calculated based on ln-transformed data*

For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Discussion and overall conclusion

The bioequivalence study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) and ICH M13A Guideline on bioequivalence for immediate-release solid oral dosage forms (EMA/CHMP/ICH/953493/2022). Widening of acceptance criteria was proposed for C_{max}. The acceptability of widening of the confidence interval for C_{max} has not been assessed since the 90% confidence interval was within 80.00-125.00%. The bioanalytical methods were adequately validated.

Bioequivalence was demonstrated between test product (Ivermectin 1% cream) and reference product (Soolantra 10 mg/g cream).

Pharmacodynamics

Ivermectin, discovered in the 1970s, is a dihydro derivative of avermectin, belonging to the macrocyclic lactone class of endectocides and consisting of a mixture of two homologous compounds, 22,23-dihydroavermectin B1a (H2B1a, not less than 80%) and 22,23-dihydroavermectin B1b (H2B1b, not more than 20%) (EMA, 2004).

Mechanistically, ivermectin exhibits anti-inflammatory effects by inhibiting lipopolysaccharide-induced production of inflammatory cytokines. Ivermectin also has anti-parasitic action, primarily through binding selectively and with high affinity to glutamate-gated chloride channels, which occur in invertebrate nerve and muscle cells (Johnson, 2020).

Originally, ivermectin introduced as a veterinary drug against a wide range of endo- and ectoparasites in commercial livestock and companion animals. Oral ivermectin has been approved for human use in the treatment and chemoprophylaxis of strongyloidiasis and onchocerciasis since 1988 in France and since 1996 in the United States.

The dual anti-inflammatory and anti-parasitic effect of Ivermectin is considered of relevance for the topical treatment of papulopustular rosacea. In detail, ivermectin targets Demodex folliculorum mites, which have been shown to reside in the pilosebaceous units of patients with papulopustular rosacea, and reduces the inflammation associated with the condition (Cardwell, et al., 2016).

The Applicant has not submitted any new primary pharmacology data, which is acceptable considering that ivermectin is a well-known compound with clinical experience both in veterinary and human.

Clinical efficacy

The applicant has not submitted any new clinical efficacy data and has instead provided a literature review on previously reported efficacy and safety data from clinical studies on papulopustular rosacea, and other clinical studies targeted in the use of oral or topical invermectin against scabies.
This is considered acceptable as ivermectin cream (10mg/g) is considered an effective and well-tolerated treatment for papulopustular rosacea. The main studies are drescribed briefly below and summarized in Table 1.

- The results of two identical 12-week long, Phase III, randomized, double-blinded studies enrolling 683 and 688 patients respectively, showed superior efficacy and comparable safety of ivermectin 10mg/g cream applied once daily as compared to vehicle control in the treatment of papulopustular rosacea. The Investigator's Global Assessment of Rosacea Severity (IGA-RS) was used as the efficacy assessment parameter. The achievement of IGA success, defined by the study as "clear" or "almost clear" rosacea severity grades, was 38.4% and 40.1% for study 1 and study 2, respectively, with the use of ivermectin 1% compared to 11.6% and 18.8% for study 1 and study 2, respectively, with the use of the vehicle control.

- In a 40-week, investigator-blinded, active controlled extension of the aforementioned studies 1 and 2, subjects that initially received ivermectin 1% cream once daily continued this regimen, whereas subjects who initially received the vehicle cream control once daily switched to azelaic acid 15% gel twice daily. In studies 1 and 2, ivermectin 10mg/g cream showed increasing efficacy from week 12 to week 52. In study 1, the percentage of patients with IGA score of “clear” or “almost clear” increased from 38.4% at week 12 to 71.1% at week 52. In study 2, the percentage of patients with IGA score of “clear” or “almost clear” increased from 40.1% at week 12 to 76.0% at week 52. Most of the patients who received ivermectin 10mg/g cream in either study 1 or study 2 denied stinging, burning, dryness, or itching associated with the medication, whereas more subjects who received azelaic acid 15% gel twice daily reported these symptoms. The initial and follow-up studies demonstrated that ivermectin 10mg/g cream is an appropriate long-term therapy for papulopustular rosacea as the medication was effective and safe for 52 weeks of treatment (*Cardwell, et al., 2016*).

Table 1. Clinical studies (*Cardwell, et al., 2016*)

Study reference	Patient characteristics	Number of participants	Medication regimen	Study design	Study duration	Findings
Stein et al[2]	Subjects >18-year-old males and females; moderate to severe PPR based on IGA; 15–70 facial inflammatory lesions	Study 1 – 683 Study 2 – 688	IVM 1% cream once daily vs vehicle cream once daily	Two multicenter studies of identical design (study 1 and study 2), randomized, double-blinded, parallel, vehicle controlled	12 weeks	**IGA success rate** IVM 1% cream Study 1 – 38.4% Study 2 – 40.1% VC Study 1 – 11.6% Study 2 – 18.8% **Adverse events incidence** IVM 1% cream Study 1 – 40.5% Study 2 – 36.5% VC Study 1 – 39.4% Study 2 – 36.5%
Stein Gold et al[21]	Subjects >18-year-old males and females; moderate to severe PPR based on IGA; 15–70 facial inflammatory lesions	Study 1 – 622 Study 2 – 636	IVM 1% cream once daily vs AzA 15% gel BID	Extension of the above study; initial IVM 1% cream groups continued IVM regimen; initial vehicle cream control group switched to AzA 15% gel twice daily	40 weeks	IVM 1% cream showed increased efficacy in study 1 and study 2 **IGA success rate** IVM 1% cream Study 1 – increased from 38.4% to 71.1% during study duration Study 2 – increased from 40.1% to 76.0% during study duration **Adverse events** IVM 1% cream Majority who received this treatment in both study 1 and study 2 denied treatment-associated stinging, burning, dryness, or itching AzA 15% gel More patients who received this treatment in both study 1 and study 2 reported treatment-associated stinging, burning, dryness, or itching
Taieb et al[22]	Subjects >18-year-old males and females; moderate to severe PPR	960	IVM 1% cream once daily vs MTZ 0.75% cream twice daily	Investigator-blinded, randomized, parallel group study	16 weeks	**Percentage reduction of inflammatory lesions** IVM 1% cream 83.0% MTZ 0.75% cream 73.7% **IGA success rates** IVM 1% cream 84.9% MTZ 0.75% cream 75.4% **Safety profile** Comparable between IVM 1% cream and MTZ 0.75% cream. Skin irritation was the most common adverse event

- In a Phase III, investigator-blinded, randomized, parallel group, superiority study of ivermectin 10mg/g cream applied once daily versus metronidazole 0.75% cream applied twice daily for the treatment of rosacea inflammatory lesions, Ivermectin cream was shwon to be superior to metronidazole 0.75% cream. A total of 962 subjects were randomized to receive Ivermectin

10mg/g (n = 478) or MTZ 0·75% (n = 484). At week 16, IVM 1% was significantly superior to MTZ 0·75% in terms of reduction from baseline in inflammatory lesions (83·0% vs. 73·7%; P < 0.001), observed as early as week 3 (Last Observation Carried Forward, LOCF). IGA results (subjects 'clear' or 'almost clear') also favoured Ivermectin 10mg/g: 84·9% vs. 75·4%, respectively (P < 0.001). Ivermectin 10mg/g cream was significantly superior to MTZ 0·75% cream and achieved high patient satisfaction (*Taieb, et al., 2015*).

- From the literature review, 57 studies were identified, with 19 providing data suitable for mixed treatment comparisons. Ivermectin 10mg/g cream QD led to a significantly greater likelihood of success compared with azelaic acid 15 % gel twice-daily (BID [relative risk (95 % credible interval): 1.25 (1.14–1.37)], and metronidazole 0.75 % cream BID [1.17 (1.08–1.29)] at 12 weeks. Ivermectin 10mg/g cream QD also demonstrated a significant reduction in inflammatory lesion count compared with azelaic acid 15 % gel BID [−8.04 (−12.69 to −3.43)] and metronidazole 0.75 % cream BID [−9.92 (−13.58 to −6.35)] at 12 weeks. Ivermectin 10mg/g cream QD led to a significantly lower risk of developing any AE or TRAE compared with azelaic acid 15% gel BID [0.83 (0.71–0.97) and 0.47 (0.32 0.67), respectively] (*Siddiqui, et al., 2016*).

Clinical safety

Studies have shown ivermectin cream to be safe with no serious adverse effects. In randomized trials, the rate of adverse effects was similar to those of vehicle, metronidazole gel, and azelaic acid, and no systemic adverse effects occurred (Table 1).

In the proposed SmPC section 4.8 it is stated that the most commonly reported adverse reactions with the ivermectin 10 mg/g cream are skin burning sensation, skin irritation, pruritus and dry skin, all occurring in 1% or less of patients treated with the medicinal product in clinical trials. They are typically mild to moderate in severity, and usually decrease when treatment is continued. No meaningful differences in the safety profile were observed between subjects 18 to 65 years and subjects ≥65 years of age

Risk Management Plan

The MAH has submitted a risk management plan v.0.3, 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 Efrinter.

Part II Safety specification

Summary of safety concerns	
Important identified risks	• Contact dermatitis (allergic or irritant)
Important potential risks	• Systemic Allergic Reactions • Accidental oral ingestion •
Missing information	• Exposure during pregnancy • Exposure during lactation • Use longer than one year • Off-label use • Use with concomitant topical treatments • Use with laser or UV radiation

Part III Pharmacovigilance Plan
Routine pharmacovigilance is suggested, and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Part V Risk minimisation measures
Routine risk minimisation is suggested, and no additional risk minimisation activities are proposed by the applicant, which is endorsed

Part VI Summary of the RMP
Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.
If important information that may affect the safe use of ivermectin is not yet available, it is listed under 'missing information' below.

Conclusion RMP assessment

The submitted Risk Management Plan, version 0.3, signed 20-01-2025 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

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

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

Periodic Safety Update Report (PSUR)
Active substance is currently listed in the published EURD list

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.

- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.

- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

Common renewal date
The common renewal date will be 5 years after closure of the DCP.

IV. BENEFIT RISK ASSESSMENT

The quality of the generic product, Efrinter, is found adequate.

There are no objections to approval of Efrinter, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated.

The product information is acceptable.

The benefit/risk is considered positive, and the application is therefore recommended for approval.

V. RECOMMENDATIONS AND CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

V.1 List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC

Post approval commitments
N/A

V.2 List of conditions pursuant to Article 21a or specific obligations pursuant to Article 22 of Directive 2001/83/EC

N/A

V.3 Summary of Product Characteristics (SmPC)

The approved SmPC is available in the MRI Product Index.

V.4 Package Leaflet (PL)

V.4.1 Package Leaflet

The approved PL is available in the MRI Product Index.

V.4.2 Assessment of User Testing

A user consultation with target patient groups on the package information leaflet (PL) has been performed for **SE/H/2399/01/DC** on the basis of a bridging report making reference to Soolantra 10 mg/g cream, SE/H/1428/01/DC regarding content
and
Ticagrelor 60/90 mg film-coated tablets (MAH Adalvo), EE/H/0338/001-002/DC regarding layout.

The bridging report submitted for **SE/H/2399/01/DC** by the applicant has been found acceptable.

VI. STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
-	-	-	-	-	-