LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Betametason/Salicylsyra Orifarm
(betamethasone dipropionate, salicylic acid)

SE/H/2255/01/DC

This module reflects the scientific discussion for the approval of Betametason/Salicylsyra Orifarm. The procedure was finalised on 2023-03-15. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Betametason/Salicylsyra Orifarm, 0,5 mg/g + 30 mg/g, ointment.

The active substances are betamethasone dipropionate and salicylic acid. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Betametason/Salicylsyra Orifarm, 0,5 mg/g + 30 mg/g, ointment, is a hybrid application (*bioequivalence cannot be demonstrated through bioavailability studies*) 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 Denmark as concerned member state (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Diprosalic 0,5 mg/g + 30 mg/g, ointment authorised in Sweden since 1978, with NV Organon as marketing authorisation holder.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

II. QUALITY ASPECTS

II.1 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.

II.2 Medicinal 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. NON-CLINICAL ASPECTS

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

Environmental Risk Assessment (ERA)
The Applicant has presented a justification for the absence of an environmental risk assessment of Betametason/Salicylsyra Orifarm which is considered acceptable. Since the product is considered essentially similar to the reference product, the introduction will not lead to an increased exposure to the environment.
There are no objections to approval of Betametason/Salicylsyra Orifarm from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
No pharmacokinetic studies have been performed for this product.

Betametason/Salicylsyra Orifarm is a product for topical application. For locally applied products, pharmacokinetic bioequivalence studies are generally not a suitable way to show therapeutic equivalence, since plasma levels are not relevant for local efficacy, although they may play a role with regard to safety. For this product conventional pharmacokinetic bioequivalence studies are not relevant due to low systemic exposure to betamethasone and salicylic acid. The absence of pharmacokinetic studies is acceptable.

Pharmacodynamics
Betametason/Salicylsyra Orifarm contains two active substances which act through different, but complementary, mechanisms of action.

Betamethasone, an analog of prednisolone, has a high degree of corticosteroid activity and a slight degree of mineralocorticoid activity. Betamethasone dipropionate belongs to a group of potent topical corticosteroids with strong anti-inflammatory, antiproliferative and immunosuppressant effects. Pharmacological doses of betamethasone help to decrease inflammation by preventing macrophage accumulation at the site of infection and interfering with leukocyte adhesion to the capillary wall.

Salicylic acid products in concentrations of 2% to 6%, alone or in combination, are and have been used for treatment of hyperkeratotic skin disorders such as psoriasis. Salicylic acid facilitates desquamation by solubilizing the intercellular cement that binds scales in the stratum corneum, thereby loosening the keratin.

Clinical efficacy

Design and conduct of clinical studies
The present application concerns an ointment formulation of betamethasone 0.5 mg/g and salicylic acid 30 mg/g indicated for treatment of psoriasis, eczema, and other steroid-sensitive dermatoses. The hybrid application for marketing authorisation is supported by one pharmacodynamic vasoconstrictor bioequivalence assay. The reference product is Diprosalic® containing betamethasone 0.5 mg/g and

salicylic acid 30 mg/g, which was approved in Sweden in 1978 in the national procedure. Supportive evidence is provided by literature data. The extent of the clinical development program is consided adequeate.

Pilot and pivotal study BDSAO/BE/06/2015
Study BDSAO/BE/06/2015 was an open label, observer blinded, randomized, single dose study of bioequivalence after topical application of the study products which was composed of a pilot part and a pivotal part. The study design was selected according to the Guidance for Industry, published by FDA in 1995 (Docket Number: FDA-2021-D-0384) and consistent with the relevant EMA guidelines.

On day 0 of both the pilot and pivotal parts of the assay, subjects came to the site, completed the "check-in" procedures and application sites on the skin were marked and randomized. The following day, day 1, validation of assay precision was performed, baseline readings were obtained, and reference product was applied topically to all subjects. Subjects participating in the study were treated by medical personnel present at the site. On day 2, skin site assessments were performed, and subjects were released from the site. Overall, the study design is according to the guideline referenced above and considered acceptable.

The primary objective of the study was to evaluate the pharmacodynamic properties and investigate bioequivalence of test product ointment containing betamethasone dipropionate (equivalent to 0.05% w/w betamethasone) and 30 mg of salicylic acid compared to the reference product. Secondary objective was to evaluate the safety and tolerability of the test and reference products.

The primary endpoint of this pharmacodynamic study was vasoconstrictor response assessed by chromameter readings and by visual assessment.

There were protocol deviations in two subjects during visual assessment procedure, these are however not considered to affect the overall assessment of the product.

Statistical aspects
The applied statistical methods in the pivotal study follow relevant EMA (and FDA, respectively) guidelines and are in general considered acceptable regarding study design and statistical analysis in this context.

Concerns have been raised regarding the two-stage design by Potvin et al. (2007, "Method C") which has not been strictly followed. Deviation from the Potvin's design was due to continuation to stage 2 (instead of stopping after stage 1). However, additional subjects were recruited in stage 2 in order to meet the criterion of 40 "detectors", i.e., subjects with RD2/RD1 $\geq$ 1.25, as recommended in the guideline applicable at the time of the study conduct. Derivation of the 90% confidence interval was according to the Locke's method used in the FDA's guidance (1995) on "Topical Dermatologic Corticosteroids: In Vivo Bioequivalence". The results of the interim analyses showed that power was <80% at the end of stage 1, and that bioequivalence was demonstrated using confidence interval at 0.0294 alpha (one-sided). After stage 2, the bioequivalence criterion was met again.

The estimates of the Test/Reference ratios are close to 100% for the primary endpoint (chromameter-based) and the supporting endpoint (visual assessment-based) and the 90% confidence intervals are well-contained within the equivalence margins (80% to 125%). Therefore, the results are considered sufficiently robust to support the bioequivalence of the test and the reference product. Further, the results indicated no systematic differences between detectors and non-detectors in the primary endpoint "Chromametric assessment".

Efficacy data and additional analyses

Pilot and pivotal study BDSAO/BE/06/2015

The pharmacodynamics vasoconstrictor bioequivalence assay *BDSAO/BE/06/2015* was performed at a single centre in Poland.

The study was performed in healthy volunteers aged 18 to 60 years of age. The total number of subjects randomized were 12 randomized subjects in the pilot part, and 60 randomized subjects in the pivotal part. 12 subjects completed the pilot part, and 57 subjects completed the pivotal part.

Most subjects were females both in the pilot and pivotal parts of the assay. Overall, demographic factors (age, height, weight, and BMI) were comparable among the treatment groups.

Pharmacodynamic results
Based on the statistical results for dose-duration response of Diprosalic ointment it was concluded that the applied Emax model adequately described pharmacodynamic vasoconstrictor effect and therefore was appropriate for the evaluation of bioequivalence between test product and reference product in the pivotal study. The calculated ED50, D1 and D2 values from Pilot Study enabled to design the pivotal part of the study.

Subgroup analysis
No subgroup analyses have been performed.

Analysis performed across trials – magnitude of treatment effect
No analysis across trials have been performed since this application concerns one clinical study.

Clinical studies in special populations
The applicant has reviewed use of topical corticosteroids and high potency topical corticosteroids in children. If possible, low potency topical corticosteroids should be used in children. However, low potency treatments may not be adequate to control the disease. and it is important that also sometimes children are effectively treated with higher potency corticosteroids. Steroid–salicylic acid combination can be used as first line of treatment on thick, scaly plaques. Betamethasone dipropionate and salicylic acid should not be used in infants and young children. The warnings regarding children in the SmPC for Diprosalic® are of relevance also for Betametason/Salicylsyra Orifarm.

Supportive evidence of efficacy
Several clinical studies which have investigated the use of the proposed combination of betamethasone and salicylic acid in claimed indications (psoriasis and other steroid-responsive dermatoses) were reviewed. Although some of the referred studies are small, it is evident that the combination has been in clinical use for decades. Betamethasone dipropionate is a potent topical corticosteroid, belonging to potency class III (according to the WHO classification of topical corticosteroids). The applicant points out that “however potent a steroid may be, it cannot exert its desired effect on the proliferating layer, unless it can penetrate the scaly barrier of the stratum corneum. A well-known aid is to use salicylic acid which, through its keratolytic action, ensures penetration of a steroid through the epidermis”. This view is endorsed.

<u>Conclusions on clinical efficacy</u>
The pilot study identified relevant exposure durations (ie, ED50, RD1, RD2) to compare the test product with the reference product regarding pharmacodynamic effects and assess the feasibility of the statistical model (Emax).

The pivotal study demonstrated bioequivalence of the pharmacodynamic effects by estimating the relative microvasoconstriction of the skin between the test product and the reference product (Diprosalic). The evidence supported by the applicant of which the performed vasoconstrictor assay is assessed as the most important are considered adequate.

However, there is also another component in the product, salicylic acid, of which no evidence can be provided for essential similarity in the performed vasoconstrictor assay. As stated by the applicant

"when used in adequate concentration, topical salicylic acid is beneficial in the management of hyperkeratotic skin disorders. When salicylic acid is used in combination with betamethasone dipropionate, it provides better corticosteroid penetration into the skin. This is crucial in the treatment of focal lesions with excessively keratinized surface."

The applicant has reviewed several clinical studies published with betamethasone and salicylic acid combination as therapy for psoriasis and similar dermatological disorders. These publications together with physical tests performed on the test product compared with the reference product (see Quality AR) can together give evidence of essential similarity of the salicylic acid component of the product.

Clinical safety
Statistical analysis indicated that the reference product was well tolerated by subjects of the pilot and pivotal part of the study.

In support if this hybrid application the Applicant conducted one pharmacodynamics vasoconstrictor bioequivalence study composed of a pilot and a pivotal part according to the Guidance for Industry, published by FDA in 1995 download (fda.gov). The reference product for this hybrid application is Diprosalic®, salva, 0,5 mg/g+30 mg/g. Moreover, published literature data were submitted.

The study is a single-site, open-label (observer blinded), randomized, controlled pilot study in twelve (12) healthy adult subjects, and pivotal study in healthy adult subjects: 60 in three cohorts and 15 in additional group. All Subjects exposed to the study at least once were part of the safety analysis. During the pilot part of the study 2 non-serious AEs were reported (classified as possibly related to the study product). Intensity of AEs were assessed as mild, and all were resolved. During the pivotal part of the study, a total of 25 non-serious AEs were reported in 25 Subjects. All were by the applicant determined as definitely related. The intensity of these AEs was classified as mild. Three subjects were withdrawn from the study due to AEs (application site allergy in two subjects, and application site hypersensitivity in one subject).

There were no deaths or serious adverse events reported during the study. There were no cases of clinically significant vital signs reported during the treatment period. There were no clinically relevant laboratory findings in either the pilot part or pivotal part of the study.

No studies in special populations have been performed which is acceptable considering the hybrid application for Betametason/Salicylsyra Orifarm.

To conclude, the performed vasoconstrictor bioequivalence assay has demonstrated bioequivalence of Betametason/Salicylsyra Orifarm to Diprosalic® ointment by Merck Sharp and Dohme GmbH, Germany (Manufacturer: SP Labo NV/SA (Belgium). The clinical parts of the proposed SmPC for Betametason/Salicylsyra Orifarm is identical to that of the reference product Diprosalic® and accepted.

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 Betametason/Salicylsyra Orifarm.

Safety specification

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

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

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

Summary of the RMP
The submitted Risk Management Plan, version 1.0 signed 08.02.2022 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.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was Portuguese.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

This is a hybrid application for approval of Betametason/Salicylsyra Orifarm.

The quality of the product Betametason/Salicylsyra Orifarm is found adequate. The performed vasoconstrictor bioequivalence assay has demonstrated bioequivalence of Betametason/Salicylsyra Orifarm to Diprosalic® ointment by Merck Sharp and Dohme GmbH, Germany (Manufacturer: SP Labo NV/SA (Belgium).

The product information is acceptable.

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

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Betametason/Salicylsyra Orifarm, 0,5 mg/g + 30 mg/g, ointment was positively finalised on 2023-03-15.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

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

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se