LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Adapalene/Benzoyl peroxide Orifarm
(adapalene, benzoyl peroxide, hydrous)

SE/H/2226/01/DC

This module reflects the scientific discussion for the approval of Adapalene/Benzoyl peroxide Orifarm. The procedure was finalised on 2023-03-01. 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, a marketing authorisation has been granted for Adapalene/Benzoyl peroxide Orifarm, 1 mg/g + 25 mg/g, Gel.

The active substance is adapalene, benzoyl peroxide, hydrous. 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 Adapalene/Benzoyl peroxide Orifarm, 1 mg/g + 25 mg/g (0,1%/2,5%), Gel, 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 DK and FI as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Epiduo, 0.1/2.5%, gel, authorised in DK since 2007, with Galderma Nordic AB 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 adapalene and benzoyl peroxide are well known. As adapalene and benzoyl peroxide are a widely used, well-known active substances, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate. There are no objections to approval of Adapalene/Benzoyl peroxide Orifarm from a non-clinical point of view.

Environmental Risk Assessment (ERA)
The Applicant has provided with an environmental risk assessment. This is in accordance with the EMA Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00). Since Adapalene/Benzoyl peroxide Orifarm is essentially similar to the reference product, this will not lead to an increased exposure to the environment.

IV. CLINICAL ASPECTS

Pharmacokinetics
No pharmacokinetic studies have been performed for this product.
Adapalene/Benzoyl peroxide Orifarm is a product for topical application and 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 adapalene and benzoyl peroxide. The absence of pharmacokinetic studies is acceptable.

Pharmacodynamics
Adapalene/Benzoyl peroxide Orifarm contains two active substances which act through different, but complementary, mechanisms of action.

Adapalene is a chemically stable, naphthoic acid derivative with retinoid-like activity. It is a potent modulator of cellular differentiation and keratinisation and has anti-inflammatory properties. Mechanistically, adapalene binds to specific retinoic acid nuclear receptors. Current evidence suggests that topical adapalene normalizes the differentiation of follicular epithelial cells resulting in decreased microcomedone formation. Adapalene inhibits the chemotactic (directional) and chemokinetic (random) responses of human polymorphonuclear leucocytes in in vitro assay models; it also inhibits the metabolism of arachidonic acid to inflammatory mediators. In vitro studies have shown inhibition of the AP-1 factors and the inhibition of the expression of toll like receptors 2. This profile suggests that the cell mediated inflammatory component of acne is reduced by adapalene.

Benzoyl peroxide has antimicrobial activity; particularly against P. acnes, which is abnormally present in the acne-affected pilosebaceous unit. Additionally, benzoyl peroxide has demonstrated exfoliative and keratolytic activities. Benzoyl peroxide is also sebostatic, counteracting the excessive sebum production associated with acne.

The pharmacodynamic properties of adapalene and benzoyl peroxide are considered well know.

Clinical efficacy

Discussion on clinical efficacy

Design and conduct of clinical studies

The present application concerns a gel formulation of adapalene 0.1% and benzoyl peroxid 2.5% indicated for treatment of mild to modest facial acne vulgaris from 9 years of age. The reference product is Epiduo® containing adapalene 0.1% and benzoyl peroxid 2.5%, which was approved in Sweden in 2008.

This is a hybrid application for approval of Adapalene/Benzoyl peroxide Orifarm, the aim of which is to bridge clinical efficacy and safety data of Adapalene/Benzoyl peroxide Orifarm to the reference product Epiduo®. Epiduo® is assessed as a relevant choice of reference product. Supportive evidence is provided by literature data.

Phase 3 study CR198-18

Study CR198-18 is a multicenter, randomized, double-blind, vehicle-controlled Phase 3 studyThe study design was selected as per recommendations stated in FDA's Draft Guidance on Adapalene 0.1% and Benzoyl Peroxide 2.5% Topical Gel. In accordance with the stated FDA guidance, this study included a reference and placebo arm as controls.

The primary objectives of the study were to evaluate the therapeutic equivalence of the test product and Epiduo® Gel in the treatment of mild to moderate facial acne vulgaris, and to demonstrate the superiority of the efficacy of the test and reference products over the placebo. The secondary objective was to evaluate the safety and tolerability of the test product in the treatment of mild to moderate facial acne vulgaris.

Eligible were patients aged 12-39 years (based on inclusion criteria), with a diagnosis of mild to moderate acne vulgaris (score of 2 or 3). The reference product Epiduo® is indicated from 9 years of age following an extension of indication Type II variation (SE/H/664/01/II/23) including subjects from 9-12 years of age (ta bort). The design of the present bridging study is considered adequate for bridging use in individuals down to 9 years of age for the test product Adapalene/Benzoyl peroxide Orifarm. The inflammatory lesions count ranged from a mean of 27.2 to 28.7, and non-inflammatory lesion counts ranged from 46.8 to 48.4. The inclusion and exclusion criteria are considered adequate to reflect the proposed therapeutic indication.

The study demonstrated that Adapalene/Benzoyl peroxide Orifarm is therapeutically equivalent to the reference product Epiduo® and that both test and reference product are superior to placebo.

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.

Long-term efficacy - duration of treatment effect

Knowledge on duration of clinical efficacy can be extrapolated to the knowledge based on clinical experience with the reference product Epiduo®.

Clinical studies in special populations

The MAH has reviewed use of adapalene and benzoyl peroxide in children 9 years and older and in adult women. Combination treatment of adapalene and benzoyl peroxide are considered well-established in both cohorts of patients since Epiduo 0.1%/2.5% gel has been on the market since 2008 in adult patients, and since 2014 in children 9 years and older.

Supportive evidence of efficacy
Treatment of acne vulgaris with adapalene as monad, or with benzoyl peroxide or with a combination of adapalene plus benzoyl peroxide were reviewed by the applicant. For a teenager with newly debuted acne vulgaris, treatment with benzoyl peroxide is often the first choice. In Sweden, several products are available containing either BPO as monad (Basiron AC® and Basiron Wash®) or in combination therapy with clindamycin (Duac®) och adapalene (Epiduo®). Similarly, the clinical experience with adapalene is extensive, which in Sweden is present as monad in Differin®, or as stated above in combination with BPO in Epiduo®. Epiduo® is in Sweden present in two different strengths 0.1 %/2.5% or 0.3 %/2.5%. The present application concerns the lower approved strength of Epiduo®.

Clinical safety
In support if this hybrid application the Applicant conducted one therapeutic equivalence study with the test product proposed for marketing, the reference product Epiduo® 0.1%/2.5% gel manufactured by Galderma, and the vehicle gel. The main safety information was derived from the study CR198-18 where acne patients received the test products once daily for 12 weeks. Moreover, published literature data were submitted.

As expected, most adverse events in the study CR198-18 were dermatological. Adverse events occurring in the test, reference, or placebo group with an incidence of > 0.5% include: General disorders and administration site conditions (7.6%, 7.0%, 0.8%, respectively), and Skin and subcutaneous tissue disorders (9.6%, 12.8%, 4.8%, respectively). Local cutaneous reactions are common following treatment with adapalene and benzoyl peroxide and were observed with both test and reference products to a similar extent which exceeds that of placebo.

No new adverse events were observed except for those previously known with the reference product Epiduo® 0.1%/2.5%. The adverse event section of the product proposed for marketing is identical to that the reference product.

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.

No laboratory evaluations were performed during the conduct of the study except serum pregnancy test which is acceptable considering the extensive clinical experience with the reference product Epiduo® and the limited systemic exposure of the active ingredients following topical application. No studies in special populations have been performed which is acceptable considering the hybrid application for Adapalene/Benzoyl peroxide 0.1%/2.5% gel. The safety sections of the SmPC proposed for Adapalene/Benzoyl peroxide 0.1%/2.5% gel is identical to that of the reference product.

Conclusions on clinical efficacy and safety
Therapeutic equivalence has been demonstrated between the test product and the reference product Epiduo®, and superiority versus placebo was shown. No new adverse events were observed except for those previously known with the reference product Epiduo® 0.1%/2.5%.

The SmPC texts proposed for Adapalene/Benzoyl peroxide Orifarm is identical to that of the reference product and is accepted.

Pharmacovigilance system
The Applicant has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

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 Adapalene/Benzoyl peroxide Orifarm.

Safety specification

The proposed SVIII.1 Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Teratogenicity
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 1.1 signed 08.08.22 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

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to Epiduo 0.1% / 2.5% gel, SE/H/664/01/DC regarding the content and Kaliumklorid Orifarm 750 mg depottabletter, DK/H/2347/001 regarding the layout.
The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

This is a hybrid application for approval of Adapalene/Benzoyl peroxide Orifarm, the aim of which is to show similarity of Adapalene/Benzoyl peroxide Orifarm to the relevant reference product Epiduo®. Therapeutic equivalence has been demonstrated between the test product and the reference product Epiduo®, and superiority versus placebo was shown. No new adverse events were observed except for those previously known with the reference product Epiduo® 0.1%/2.5%.

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 Adapalene/Benzoyl peroxide Orifarm, 1 mg/g + 25 mg/g, Gel was positively finalised on 2023-03-01.

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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)

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