LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Epiduo
(Adapalene 0.1% and Benzoyl peroxide 2.5%)

SE/H/664/01/DC

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.mpa.se E-mail: registrator@mpa.se

This module reflects the scientific discussion for the approval of Epiduo. The procedure was finalised at 2007-11-28. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Galderma has applied for a marketing authorisation for Epiduo, gel, adapalene 0.1% and benzoyl peroxide 2.5%. Adapalene and benzoyl peroxide have marketing authorisations in Sweden for treatment of acne in similar or higher strengths as separate products. Adapalene is available as Differin® (adapalene) 0.1% gel, cream, or solution. Benzoyl peroxide is marketed under a number of different trade names - including Cutacnyl® and Benzac® AC - and in a variety of topical formulations with concentrations which range from 2.5% to 20%.

For approved indications, see Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Epiduo is presented in the form of gel containing 1mg of adapalene and 25 mg of benzoyl peroxide per gram of the formulation. The excipients are disodium edetate, docusate sodium, glycerol, poloxamer, propylene glycol, water and Simulgel 600 PHA. The gel is filled in tube consisting of polypropylene/polyethylene/aluminium.

II.2 Drug Substance

Benzoyl peroxide has a monograph in the Ph. Eur. The drug substance is a white, granular powder which is insoluble in water and sparingly soluble in alcohol, acetone and ether. The structure of benzoyl peroxide has been adequately proven and its physico-chemical properties sufficiently described. No chiral centre is present in the structure of benzoyl peroxide. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

Adapalene does not have a monograph in the Ph. Eur. Adapalene is a white to off white powder which is practically insoluble in water. The structure of adapalene has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on polymorphism, chirality, is presented. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The specifications of the active substances include relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.
Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Epiduo gel is formulated using excipients described in the current Ph Eur, except for simulgel 600 PHA which is controlled according to acceptable in house specifications. All raw materials used in the product are of vegetable origin
The product development has taken into consideration the physico-chemical characteristics of the active substance.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.
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 under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, when stored below 30 ^{o}C.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

Epiduo Gel contains two active ingredients, benzoyl peroxide and adapalene, with different mechanisms of action which are thought to act complementarily in the treatment of *Acne vulgaris*. The product contains a new excipient, the gelling agent Simulgel 600 PHA, which does not influence the pharmacodynamic properties of adapalene, and it is considered unlikely that it would affect the pharmacodynamic properties of the combination adapalene/benzoyl peroxide.

III.2 Pharmacokinetics

The pharmacokinetics of the individual components is considered well known. When applied on the skin only small amounts of adapalene are absorbed. Benzoyl peroxide is rapidly converted to benzoic acid which is excreted in urine. Performed absorption/metabolism studies with the combination of adapalene 0.1% and benzoyl peroxide 2.5% did not demonstrate any different absorption/metabolism properties when the active ingredients are administered together compared to when administered alone.

III.3 Toxicology

The toxicology of the active ingredients is considered well known. In support of the application, the applicant has performed several pharmacokinetic and toxicological studies with the final formulation.

Dermal toxicity studies have been conducted in rats (4 weeks), dogs (4 week) and minipigs (4 and 13 week study durations). No signs of systemic induced toxicity were noted in any animal species. Local reactions of varying seriousness were noted in the rat, dog and minipig and are expected considering the irritant properties of both adapalene and benzoyl peroxide when administered alone. No irritant property was noted in vehicle groups treated with the gel base in studies up to 13 weeks duration (minipig). Toxicokinetic data of adapalene demonstrate systemic uptake in the rat, dog and minipig. In humans, low levels of adapalene have been detected in a few patients treated with Epiduo gel. The animals showed considerably higher systemic exposure, and it can be concluded that they have been sufficiently exposed to the combination adapalene 0.1% and benzoyl peroxide 2.5%.

The local tolerance of the combination adapalene 0.1% and benzoyl peroxide 2.5% was evaluated in three studies with a prototype formulation considered representative for the to-be-marked formulation. The prototype formulation showed irritant ability in a dermal irritation test on rabbit skin, which is an expected finding considering the local irritant properties of the individual components. No phototoxic potential or photo allergenic potential was noted when investigated in rabbits. The combination adapalene 0.1% and benzoyl peroxide 2.5% induced positive skin sensitization reaction in guinea pigs under maximised conditions.

The absence of new genotoxicity studies on adapalene and benzoyl peroxide is accepted considering the well known profile of the active ingredients. The profiles are not considered to be altered when the active substances are administered together.

The absence of new carcinogenicity study is acceptable considering the well known profile of the active ingredients.

The absence of new teratogenicity study is acceptable considering the well known profile of the active ingredients. Adapalene has showed teratogenicity like other retinoids only after oral administration corresponding to high systemic exposures but not after topical treatments in animal studies. Benzoyl peroxide has not showed teratogenicity in animal studies

The absence of safety concerns regarding dermal or systemic toxicity of Simulgel 600 PHA has been documented in the application.

III.4 Ecotoxicity/environmental risk assessment

An environmental risk assessment which stopped in Phase I was submitted. The available data do not exclude potential environmental concerns and the ERA needs to be supplemented, which was handled as a Follow Up Measures.

III.5 Discussion on the non-clinical aspects

From a non-clinical point of view no safety concerns for humans at the proposed indication have been identified.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

The pharmacokinetic documentation for Epiduo gel comprises three *in vitro* studies and two *in vivo* studies. The *in vitro* studies were mainly of explorative nature, but indicate no difference in absorption of the active components whether administered in combination or as single components. The *in vivo* studies were performed in patients with *acne vulgaris* and involved application of the gel once daily on a 1000 cm^2 application area for 10 or 30 days. Only adapalene plasma concentrations were assessed. In the 10-day study, the LOQ for adapalene was rather high and very few subjects had measurable concentrations. In the 30-day study, a method with a lower LOQ (0.1 ng/ml) was used and a few more quantifiable concentrations were observed, although most subjects had concentrations below LOQ. The highest $AUC_{0\text{-}24h}$ value observed in different individuals was 1.99 ng.h/ml for the fixed combination.

In conclusion, both the *in vitro* and the *in vivo* studies have demonstrated a low absorption of adapalene from the combination product and there appears to be no difference in comparison with a formulation containing only adapalene.

IV.2 Pharmacodynamics

Epiduo combines two active substances, which act through different, but complementary, mechanisms of action.
Adapalene is a chemically stable, naphthoic acid derivative with retinoid-like activity. Biochemical and pharmacological profile studies have demonstrated that adapalene acts in the pathology of Acne vulgaris as a modulator of cellular differentiation and keratinisation and it has anti-inflammatory properties.

Benzoyl peroxide has been shown to have 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.

IV.3 Clinical efficacy

One pivotal study, **study 18094**, has been submitted. To further support the efficacy results seen in the pivotal study, and to assess the long-term use of adapalene 0.1%/benzoyl peroxide 2.5% Gel, a one-year, open-label, safety and efficacy study involving 452 subjects with acne vulgaris has been carried out (**study 18089**). The characteristics of the populations studied in these clinical trials were similar.

A Phase 1, PK study in 24 subjects with acne vulgaris is also included in the evaluation of efficacy (**study 18097**) since this study recruited subjects with acne vulgaris and included the evaluation of efficacy after 30 days of treatment (based on Percent Change in Inflammatory, Non-inflammatory and Total Lesion Counts) so the data can be considered supportive.

Study	Full Title	Abbreviated Title
RD.06.SRE.18094 EU Pivotal Study	A Multi-Centre, Randomised, Double-Blind, Parallel Group Study to Evaluate the Safety and Efficacy of a Fixed Combination of Adapalene 0.1% and Benzoyl Peroxide 2.5% (Adapalene and Benzoyl Peroxide Topical Gel) Gel Compared to Each Monad and Topical Gel Vehicle in Subjects with Acne Vulgaris	Efficacy and Safety Study
RD.06.SRE.18089 Phase 3	A Long Term Safety and Efficacy Study of a Fixed Combination of Adapalene 0.1% and Benzoyl Peroxide 2.5% (Adapalene and Benzoyl Peroxide Topical Gel) Gel in Subjects with Acne Vulgaris.	Long-Term Safety Study
RD.06.SRE.1809 Phase 1	A Pharmacokinetic Study to Determine the Systemic Exposure to Adapalene During Dermal Application of Either a Fixed-Combination of Adapalene 0.1% and Benzoyl Peroxide 2.5% (Adapalene and Benzoyl Peroxide Topical Gel) Gel or Adapalene 0.1% Topical Gel for 30 Days in Subjects with Acne Vulgaris.	Thirty-Day PK Study

Efficacy conclusion

In the treatment of acne, a combination of the two already approved components, adapalene 0.1% and benzoyl peroxide 2.5% applied once daily may be of benefit to the patient provided that sufficient efficacy and in particular skin safety are proven.

Epiduo has been adequately studied and the submitted documentation contains relevant clinical studies of efficacy comparing Epiduo with the included monads, adapalene 0.1% and benzoylperoxide 2.5% and with vehicle. One pivotal study was performed to prove efficacy, which was reached. Dermal safety studies have been performed. The choice of dose included in the combination product was based on level of skin irritation in these studies. The choice of comparators was based on the active ingredients in the combination product and was given as once daily dosing. Adapalene dose and concentration are in accordance with previous approval but benzoyl peroxide was compared in a low concentration 2.5% and with dosing once daily instead of twice daily.

The irritative properties of both adapalene and benzoylperoxide are well known and also often make treatment compliance difficult. To combine both drugs in the treatment of acne is common in clinical practice, with individual adjustments of dosing frequency and latency between applications. The proposed dose and the concentrations chosen were based on studies where mainly the skin irritating properties were limiting to higher concentrations and frequency of dosing. The approach to use skin safety to define the dose is relevant and the appropriateness of the chosen doses is sufficiently shown. However, the choice of comparators could be elaborated on. Efficacy of a combination product should be shown towards the included components. In the performed pivotal study, efficacy has been shown towards each individual component and also towards placebo vehicle. A shortcoming, in addition to the once daily dosing of benzoyl peroxide, is the choice of the monads which consist of the same vehicle as the applied combination product, thus a non-approved comparator. The MAH presents an efficacy discussion dealing with these issues, which is relevant (see summary in clinical assessment). No major differences between the approved products and the monads are expected. Despite the shortcomings, efficacy is considered adequately shown with adapalene 0.1% / benzoyl peroxide 2.5% towards placebo vehicle, but also towards both the monads. Convincing efficacy was proven versus the separate comparators. Efficacy has therefore been sufficiently shown.

Summary of Baseline Lesion Count and Percent Change in Inflammatory, Noninflammatory and Total Lesion Counts in Study RD.06.SRE.18094 (ITT Population)

	Adapalene/BPO Gel N=149		Adapalene Monad N=148		BPO Monad N=149		Gel Vehicle N=71	
	Median	Mean	Median	Mean	Median	Mean	Median	Mean
Inflammatory Lesions								
Baseline	27	29.7	28	29.1	28	30.5	29	31.1
Week 12 LOCF	-62.79%	-52.41%	-45.71%	-39.91%	-43.59%	-35.82%	-37.84%	-31.84%
Noninflammatory Lesions								
Baseline	44.0	51.5	45.0	51.1	43.0	46.8	46.0	49.9
Week 12 LOCF	-51.22%	-45.88%	-33.33%	-29.59%	-36.36%	-32.17%	-37.50%	-27.84%
Total Lesion Count								
Baseline	78.0	81.2	75.0	80.2	74.0	77.3	78.0	81.1
Week 12 LOCF	-51.02%	-48.55%	-35.40%	-33.99%	-35.59%	-33.32%	-31.03%	-29.66%

Summary of Co-Primary Endpoints of Success Rate in Study RD.06.SRE.18094 (ITT Population)

Parameters	Adapalene/BPO Gel	Adapalene Monad	BPO Monad	Gel Vehicle

Success Rate	27.5%	15.5%	15.4%	9.9%

Summary of P-Values for Success Rate and Percent Change in Lesion Counts in Study RD.06.SRE.18094 (ITT Population)

	Adapalene/BPO Gel		
	versus Adapalene Monad	**versus BPO Monad**	**versus Gel Vehicle**
ITT population: Week 12 (LOCF)			
Success Rate[a]	0.008	0.003	0.002
Percent Change[b]			
Inflammatory	<0.001	<0.001	<0.001
Noninflammatory	<0.001	<0.001	<0.001
Total	<0.001	<0.001	<0.001
PP population: Week 12 (LOCF)			
Success rate[a]	0.019	<0.001	0.011
Percent Change[b]			
Inflammatory	0.007	<0.001	<0.001
Noninflammatory	0.001	<0.001	0.012
Total	<0.001	<0.001	<0.001

Source: **RD.06.SPR.18094** Table 12, Mod. 5, Vol. 8
LOCF = Last Observation Carried Forward
[a] p-values were based on CMH test general association statistic, controlling for centre
[b] p-values were based on CMH test row mean difference, RIDIT transformed score, controlling for centre

IV.4 Clinical safety

The development of the combination product, Epiduo, and the documentation submitted, is based on experience from the previously, for acne, approved active components adapalene and benzoyl peroxide. Studies have been performed with the combination product in comparison with each component and also vehicle. Safety studies including dermal safety studies have been performed. The performed dermal safety studies confirm the already well known irritative properties of the components, but do not indicate phototoxicity/photosensitivity. Literature data are somewhat contradictory on the phototoxicity/sensitivity potential. Results from the dermal safety studies, confirm that the combination product is sufficiently safe and with a similar skin safety profile as the two active ingredients administered as monoproducts. The local irritant effect is well known

No new unknown side-effects were identified in the submitted safety documentation for Epiduo. The already well known properties and the side-effect profile were confirmed. The side-effects were acceptable with the new combination of the two components, benzoylperoxide 2.5% and adapalene 0.1%, with the proposed once daily dosing regimen.

To avoid skin irritancy, the product should be used in line with the previously approved single components, i.e. individual adjustments of dose intervals might be needed, due to skin irritancy occurring in periods. Treatment might be interrupted for a few days and periods with dry skin

might need application of skin moisturers. These temporary changes in "treatment habits" are well known and acceptable in patients when treating acne.

The pharmacovigilance/risk management systems seem adequate as well as the description of potential risks already well known for the two active components. Proposal for continuous follow-up is acceptable.

IV.5 Discussion on the clinical aspects

See section V below.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Epiduo is a combination of two well known and marketed components in the treatment of acne.

Nonclinical dermal toxicity studies in the rat, dog and minipig showed no signs of systemic induced toxicity. Local reactions at the administration site were observed and are expected considering the irritant properties of both adapalene and benzoyl peroxide when administered alone.

The systemic absorption of adapalene from the combination product is low and there appears to be no difference in comparison with a formulation containing only adapalene.

Efficacy of the combination product has been shown towards placebo and the two monads. Safety is mainly concerning skin irritancy, which is also known properties of the included substances. The SPC adequately reflects the present knowledge of safety of a retinoid-like compound which is administered via the dermal route.

User testing of the package leaflet has been performed.

The risk/benefit ratio is considered positive and Epiduo, gel, adapalene 0.1% and benzoylperoxide 2.5% is recommended for approval.

Follow-up measures that were agreed upon can be seen below.

Area[1]	**Description**
Quality	Batch analysis data on two consecutive batches to be produced at GPCI, intended site for the manufacture of commercial batches, should be submitted. Analytical data and Certificates of Analysis on these two additional industrial batches will be communicated in February 2008 and subsequently submitted in CTD update.
Non-clinical	The Applicant commits to provide a revised Environmental Risk Assessment according to guideline CHMP/SWP/4447/00 as post-approval commitment, in agreement with the Reference Member State. A stepwise testing strategies approach will be adapted to the specific properties of each drug substance. The corresponding

	study reports will be made available to the agency as part of the post-approval commitment.

1. Areas: Quality, Non-clinical, Clinical, Pharmacovigilance

VI. APPROVAL

The Mutual recognition/Decentralised procedure for Epiduo, gel, adapalene 0.1% and benzoylperoxide 2.5% was successfully finalised on 20071128.

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Public Assessment Report – Update

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)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
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