Medicines & Healthcare products
Regulatory Agency

Public Assessment Report

National Procedure

Adapalene/Benzoyl Peroxide 0.1%/ 2.5% Gel

adapalene
benzoyl peroxide, hydrous

PL 56328/ 0001

Penlan Pharmaceuticals Limited

LAY SUMMARY

Adapalene/Benzoyl Peroxide 0.1%/ 2.5% Gel
Adapalenebenzoyl peroxide, hydrous

This is a summary of the Public Assessment Report (PAR) for Adapalene / Benzoyl Peroxide. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as Adapalene / Benzoyl Peroxide in this lay summary for ease of reading.

This product has been authorised by Medicines and Healthcare products Regulatory Agency (MHRA) for the United Kingdom. This procedure takes into account the outcome of a decentralised (DC) procedure in European Union Member States (and/or Iceland, Liechtenstein, Norway) on 20 December 2021 (HR/H/0197/001/DC). This is known as the MR/DC Reliance Procedure.

This application was approved under Regulation 52B of the Human Medicines Regulation 2012, as amended (previously Article 10.3 of Directive 2001/83/EC, as amended).

For practical information about using Adapalene / Benzoyl, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Adapalene / Benzoyl and what is it used for?
This medicine is used for the treatment of acne.

How does Adapalene / Benzoyl work?
This gel combines two active ingredients, adapalene and benzoyl peroxide, which work together but in different ways:

- Adapalene belongs to a group of products known as retinoids and acts specifically on the skin processes that cause acne.
- The other active ingredient, benzoyl peroxide, works as an antimicrobial agent and by softening and peeling the outer layer of the skin.

How is Adapalene / Benzoyl used?
The pharmaceutical form of this medicine is a gel and the route of administration is placed on the skin (a topically applied gel / cutaneous use).

Due to the high-level of detail in the usage instructions it is best to refer directly to the PIL and Summaries of Product Characteristics (SmPCs) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website, for information on how Adapalene / Benzoyl is used.

This medicine can only be obtained with a prescription.

The patient should always take the medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Adapalene / Benzoyl have been shown in studies?
Because Adapalene / Benzoyl is a hybrid medicine, studies in patients with mild to moderate facial acne consist of tests to determine that it is therapeutically equivalent to the reference medicine.

What are the possible side effects of Adapalene / Benzoyl?
For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Because Adapalene / Benzoyl is a hybird medicine and is therapeutically equivalent to the reference medicine, its benefits and possible side effects are considered to be the same as the reference medicine.

Why was Adapalene / Benzoyl approved?
It was concluded that, Adapalene / Benzoyl has been shown to be comparable to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Adapalene / Benzoyl?
As for all newly-authorised medicines, an Risk Management Plan (RMP) has been developed for Adapalene / Benzoyl. The RMP details the important risks of Adapalene / Benzoyl, how these risks can be minimised, any uncertainties about Adapalene / Benzoyl (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Adapalene / Benzoyl:

Summary of safety concerns	
Important identified risks	• Hypersensitivity
Important potential risks	• Teratogenic effects due to absorption of adapalene in pregnant women
Missing information	• None

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Adapalene / Benzoyl are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Other information about Adapalene / Benzoyl
A marketing authorisation was granted in the United Kingdom on 7 June 2024.

The full PAR for Adapalene / Benzoyl follows this summary.

This summary was last updated in November 2024.

TABLE OF CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Adapalene/Benzoyl Peroxide 0.1%/ 2.5% Gel (PL 56328/ 0001) could be approved.

The product is approved for the following indications:
Cutaneous treatment of *acne vulgaris* when comedones, papules and pustules are present.

Adapalene/ Benzoyl Peroxide 0.1% / 2.5% Gel is indicated in adults, adolescents and children aged 9 years and over.

Adapalene + Benzoyl Peroxide 0.1% + 2.5% Gel combines two active substances, which act through different, but complementary, mechanisms of action:

- ***Adapalene***: Adapalene is chemically stable, naphtoic acid derivative with retinoid-like activity. Biochemical and pharmacological profile studies have demonstrated that adapalene acts in the pathology of *acne vulgaris*: it is a potent modulator of cellular differentiation and keratinisation and it 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 (BPO):*** Benzoyl peroxide has been shown to have antimicrobial activity; particularly against *Cutibacterium acnes*, which is abnormally present in the acne-affected pilosebaceous unit. The mechanism of action of Benzoyl peroxide has been explained by its highly lipophilic activity, enabling its penetration through the epidermis into bacterial and keratinocyte cell membranes of the pilosebaceous unit. Benzoyl peroxide is recognized as a very effective broad-spectrum antibacterial agent in the treatment of acne vulgaris. It has been demonstrated to exert bactericidal effect by generating free radicals that oxidize proteins and other essential cellular components in the bacterium wall. The minimum inhibitory concentration of benzoyl peroxide is bactericidal and has demonstrated effectiveness on antibiotic-sensitive and antibiotic-resistant C. acnes strains. Additionally, benzoyl peroxide has demonstrated exfoliative and keratolytic activities.

This product has been authorised by Medicines and Healthcare products Regulatory Agency (MHRA) for the United Kingdom. This procedure takes into account the outcome of a decentralised (DC) procedure in European Union Member States (and/or Iceland, Liechtenstein, Norway) on 20 December 2021 (HR/H/0197/001/DC). This is known as the MR/DC Reliance Procedure. For the scientific discussion of the quality, non-clinical and clinical assessment conducted during the MR and/or DC procedures, please refer to the Reference Member State (RMS) Public Assessment Report, available on the RMS regulatory agency website or on the Heads of Medicines Agencies website.

This application was approved under Regulation 52B of the Human Medicines Regulation 2012, as amended (previously Article 10.3 of Directive 2001/83/EC, as amended).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

A marketing authorisation was granted on 7 June 2024

II. PRODUCT INFORMATION

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

The SmPC is in line with current guidelines and is satisfactory.

PATIENT INFORMATION LEAFLET (PIL)

The PIL is in line with current guidelines and is satisfactory.

LABEL

The labelling is in line with current guidelines and is satisfactory.

III. QUALITY ASPECTS

MHRA considered that the quality data submitted for this application is satisfactory.

The grant of a marketing authorisation was recommended.

IV. NON-CLINICAL ASPECTS

MHRA considered that the non-clinical data submitted for this application is satisfactory.

The grant of a marketing authorisation was recommended.

V. CLINICAL ASPECTS

This is a hybrid application under Regulation 52 for a topical fixed dose combination product of adaplene 0.1%/benzoylperoxide 2.5% gel for use in acne vulgaris with the reference medicinal product of Epiduo 0.1%/2.5% gel.

As BE studies are not appropriate to demonstrate equivalence between the proposed product and the reference medicinal product, the applicant has submitted a clinical therapeutic equivalence study to demonstrate the equivalence of the proposed product and the reference medicinal product.

The study was a double-blind, randomized, parallel group, placebo and active controlled (Epiduo Gel) study in subjects with mild to moderate facial acne vulgaris to show non-inferiority of the test product and the reference product on the primary endpoint of mean percent change from baseline to week 12 in the inflammatory and non-inflammatory lesion count. Secondary endpoints were:

- Proportion with a clinical response of success at week 12
- Percentage of subjects who achieved at least 50% reduction in lesion counts and
- Investigator’s evaluation for improvement

Equivalence was concluded if the 90%confidence interval for the test to reference difference was within the interval 80.00% to 125.00% in the per protocol (PP) population.
The study was conducted across 19 study sites in India. The study design and methodology are consistent with the FDA guidance. As there is no product specific guidance in Europe, the use of the FDA guidance is considered appropriate.

A total of 650 patients were randomised in a 2:2:1 ratio to Test:reference:placebo. A total of 1 subjects withdrew. The modified intent-to-treat (mITT) population (n=615) included all patients who had applied at least one dose of investigational study treatment. The per protocol (PP) population (n=465) included all subjects who returned to the study site for the week 12 visit within a +/- 4 days window and whose treatment compliance fell between 75% and 100%, and who did not have any major protocol deviation.

The results for the primary endpoints are below

Table 7. Study CR198-18; Results of statistical analysis (equivalence and superiority to placebo) for primary outcome **'inflammatory lesions count'** (in percentage of population's LS means).

PP population	**Test**	**Reference**	**Placebo**
N	183	185	97
Change in inflammatory lesion	-78.1%	-78.3%	-52.3%
Standardized ratio	100.20%		
90%CI for standardized ratio	96.21 – 104.19%		
mITT population	**Test**	**Reference**	**Placebo**
N	250	239	126
Change in inflammatory lesion	-77.4%	-75.3%	-50.2%
Change in inflammatory lesion vs. Placebo	-22.20%	-25.08%	
Standardized ratio for T. and R. vs. Placebo	97.89%		
90%CI for T. and R. standardized ratio vs. Placebo	93.93 – 101.84%		
P-value vs. Placebo	< 0.001	<0.001	

Table 8. Study CR198-18; Results of statistical analysis (equivalence and superiority to placebo) for primary outcome **'non-inflammatory lesions count'** (in percentage of population's LS means).

PP population	**Test**	**Reference**	**Placebo**
N	183	185	97
Change in non-inflammatory lesion	-69.6%	-68.4%	-42.0%
Standardized ratio T. vs. R.	98.82%		
90%CI for standardized ratio T. vs. R.	94.89 – 102.74%		
mITT population	**Test**	**Reference**	**Placebo**
N	250	239	126
Change in non-inflammatory lesion	-69.6%	-68.4%	-42.0%
Change in non-inflammatory lesion vs. Placebo	-28.71%	-26.40%	

Standardized ratio for T. and R. v. Placebo	97.69%		
90%CI for T. and R. standardized ratio vs. Placebo	94.11 – 101.28%		
P-value vs. Placebo	< 0.001	<0.001	

Equivalence of test and reference was demonstrated on the primary endpoint and both the actives were superior to placebo.

No major concerns were identified in the conduct or reporting of the study by the reference member state (RMS). Apart from the fact that the results are very narrow indicating low variability, which is surprising for a topical product, there are no major concerns identified in the UK assessment. This is a very low risk product and the data have been accepted by the RMS.

All the secondary endpoints were supportive of the inference of equivalence drawn based on the primary endpoint. Safety profile of both test and reference were comparable.
Overall, the study demonstrated that the test product is therapeutically equivalent to the reference and both these products were superior to placebo confirming assay sensitivity.

The grant of a marketing authorisation was recommended.

VI. RISK MANAGEMENT PLAN (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

VII. USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) was provided with the application in accordance with legal requirements, including user consultation.

VIII. OVERALL CONCLUSION, BENEFIT/RISK AND RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The benefit/risk balance is, therefore, considered to be positive.

The Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and labelling are satisfactory.

In accordance with legal requirements, the current approved UK versions of the SmPCs and PIL for these products are available on the MHRA website.

IX. TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations, where significant changes are made, are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPCs and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**