Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Clindamycin + Benzoyl Peroxide 10 mg/g + 50 mg/g Gel

Clindamycin phosphate and Benzoyl Peroxide, Hydrous

PL 35533/0164

Aspire Pharma Limited

LAY SUMMARY

Clindamycin + Benzoyl Peroxide 10 mg/g + 50 mg/g Gel
Clindamycin phosphate and Benzoyl Peroxide, Hydrous

This is a summary of the Public Assessment Report (PAR) for Clindamycin + Benzoyl Peroxide 10 mg/g + 50 mg/g Gel. 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 Clindamycin phosphate and Benzoyl Peroxide Gel in this lay summary for ease of reading.

For practical information about using Clindamycin phosphate and Benzoyl Peroxide Gel, patients should read the package leaflet or contact their doctor or pharmacist.

What is Clindamycin phosphate and Benzoyl Peroxide Gel and what is it used for?
This application is for a hybrid medicine. This means that the medicine is similar to a reference medicine already authorised in the European Union (EU) called Duac Once Daily 10mg/g + 50mg/g Gel.

Clindamycin phosphate and Benzoyl Peroxide Gel is used for treating mild to moderate acne on the skin.

How does Clindamycin phosphate and Benzoyl Peroxide Gel work?
This medicine contains the active ingredients clindamycin and benzoyl peroxide. Clindamycin is an antibiotic which stops the bacteria involved in acne from reproducing. Benzoyl peroxide reduces blackheads and whiteheads. It also kills the bacteria involved in acne.

How is Clindamycin phosphate and Benzoyl Peroxide Gel used?
The pharmaceutical form of this medicine is a gel and the route of administration is cutaneous (on the skin).

Clindamycin phosphate and Benzoyl Peroxide Gel should be used once a day in the evening. It may take 2 to 5 weeks to see the effect of this medicine. This medicine must not be used for more than 12 weeks at one time. A doctor will tell the patient how long their treatment will last.

To apply this medicine, patients should completely remove any make-up and should wash the affected area of skin well, rinse with warm water and gently pat dry. Patients should put a thin film of gel on the entire area of affected skin, using their fingertips. They should apply the gel to all of the areas of the skin which have acne, not just to the individual spots. If the gel does not rub into the skin easily, patients are using too much.

When used for the face only, an amount of gel from the tube which reaches from the tip of the finger to the first joint (the first crease on the finger) should be used. This is a ‘fingertip’.

When used for the face and back, two and a half ‘fingertips’ in total should be used.

If the patient gets a lot of dryness or skin peeling, they can use an oil-free, fragrance free, hypoallergenic moisturiser, use Clindamycin phosphate and Benzoyl Peroxide Gel less

frequently or stop treatment for a short period, to allow the skin to adjust to the treatment. This medicine may not work properly if it is not applied every day.

Patients should wash their hands after using the gel. After the gel has dried, patients can use a non-greasy make-up.

For further information on how Clindamycin phosphate and Benzoyl Peroxide Gel is used, refer to the package leaflet and Summary/Summaries of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can be obtained without a prescription.

The patient should always take this 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 Clindamycin phosphate and Benzoyl Peroxide Gel have been shown in studies?
Because Clindamycin phosphate and Benzoyl Peroxide Gel is a hybrid medicine, studies consist of laboratory-based tests to determine that it is therapeutically equivalent to the reference medicine.

What are the possible side effects of Clindamycin phosphate and Benzoyl Peroxide Gel?
Because Clindamycin phosphate and Benzoyl Peroxide Gel is a hybrid medicine and is therapeutically equivalent to the reference medicine, its benefits and possible side effects are taken as being the same as the reference medicine.

For the full list of all side effects reported with this medicine, see Section 4 of the package leaflet or the Summary of Product Characteristics (SmPC) available on the MHRA website.

Why was Clindamycin phosphate and Benzoyl Peroxide Gel approved?
It was concluded that, in accordance with EU requirements, Clindamycin phosphate and Benzoyl Peroxide Gel has been shown to be therapeutically equivalent 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 Clindamycin phosphate and Benzoyl Peroxide Gel?
A Risk Management Plan (RMP) has been developed to ensure that Clindamycin phosphate and Benzoyl Peroxide Gel is used as safely as possible. Based on this plan, safety information has been included in the SmPC and the package leaflet, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously.

Other information about Clindamycin phosphate and Benzoyl Peroxide Gel
A Marketing Authorisation for Clindamycin phosphate and Benzoyl Peroxide Gel was granted in the UK on 11 March 2021.

The full PAR for Clindamycin phosphate and Benzoyl Peroxide Gel follows this summary. This summary was last updated in April 2021.

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 Clindamycin + Benzoyl Peroxide 10 mg/g + 50 mg/g Gel (PL 35533/0164) could be approved.

The product is approved for the following indication(s):
The topical treatment of mild to moderate acne vulgaris, particularly inflammatory lesions, in adults and adolescents aged 12 years and above. Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Clindamycin is a lincosamide antibiotic with bacteriostatic action against Gram-positive aerobes and a wide range of anaerobic bacteria. Lincosamides such as clindamycin bind to the 23S subunit of the bacterial ribosome and inhibit the early stages of protein synthesis. The action of clindamycin is predominantly bacteriostatic although high concentrations may be slowly bactericidal against sensitive strains.

Benzoyl peroxide is mildly keratolytic acting against comedones at all stages of their development. It is an oxidising agent with bactericidal activity against Propionibacterium acnes, the organism implicated in acne vulgaris. Furthermore, it is sebostatic, counteracting the excessive sebum production associated with acne.

Clindamycin + Benzoyl Peroxide Gel has a combination of mild keratolytic and antibacterial properties providing activity particularly against inflamed lesions of mild to moderate acne vulgaris.

This application was submitted under Article 10(3) of Directive 2001/83/EC, as amended, claiming to be a hybrid medicinal product of a suitable originator product, Duac Once Daily 10mg/g + 50mg/g Gel, that has been licensed within the EU for a suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the application is based on being a hybrid medicinal product of a reference product that has been licensed for over 10 years.

A biowaiver was submitted with this application which was accepted. No clinical bioequivalence or therapeutic equivalence studies were required, and none were provided with this application.

Acceptable data supporting equivalence between the test and reference products has been provided in the form of comparative *in-vitro* release testing (IVRT) data along with two supportive *in vitro* studies using human skin. These studies were conducted in-line with current Good Laboratory Practice (GLP).

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 national marketing authorisation was granted in the UK on 11 March 2021.

II QUALITY ASPECTS

II.1 Introduction

This product consists of a white to slightly yellow homogeneous gel. Each 1 g of gel contains 10 mg clindamycin as clindamycin phosphate and 50 mg anhydrous benzoyl peroxide as hydrous benzoyl peroxide.

In addition to clindamycin and benzoyl peroxide this product also contain the excipients carbomer (50000mPa.s), dimeticone (100mm2.s-1), disodium lauryl sulfosuccinate, edetate disodium, glycerol, silica (colloidal hydrated), poloxamer 182, purified water and sodium hydroxide.

The finished product is packaged in internally lacquered membrane-sealed aluminium tubes fitted with polyethylene screw-caps, packed into a cartons in pack sizes of 25, 30, 50 and 60 grams. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

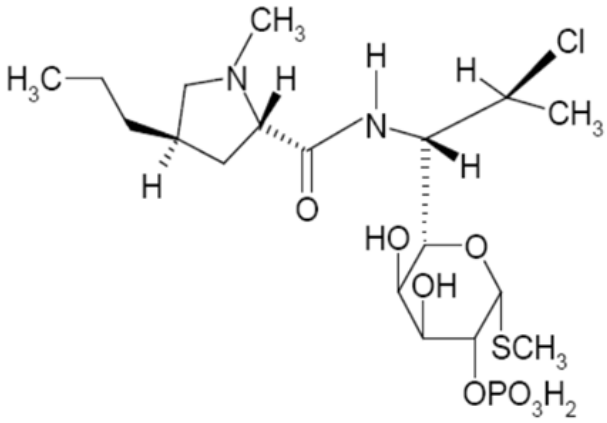
II.2 ACTIVE SUBSTANCES

rINN: Clindamycin phosphate

Chemical Name: 2S,4R)-N-[(1S,2S)-2-chloro-1-[(2R,3R,4S,5R,6R)-3,4,5-trihydroxy-6-methylsulfanyloxan-2-yl]propyl]-1-methyl-4-propylpyrrolidine-2-carboxamide

Molecular Formula: $C_{18}H_{33}ClN_2O_5S$

Chemical Structure:



Molecular Weight: 505.0

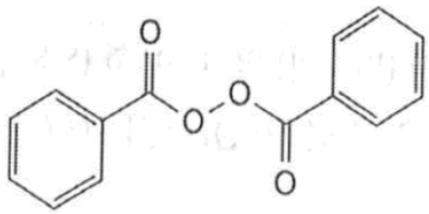
Appearance: White or almost white, slightly hygroscopic powder

Solubility: Freely soluble in water, very slightly soluble in ethanol (96 per cent), practically insoluble in methylene chloride

Clindamycin phosphate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

rINN: Benzoyl peroxide, hydrous
Chemical Name: benzoyl benzenecarboperoxoate
Molecular Formula: $C_{14}H_{10}O_4$
Chemical Structure:



Molecular Weight: 242.2 for anhydrous substance
Appearance: White or almost white, granular (crystalline) powder
Solubility: Practically insoluble in water, soluble in acetone, soluble in methylene chloride with the separation of water, slightly soluble in ethanol (96 per cent)

Benzoyl peroxide, hydrous, is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 DRUG PRODUCT

Pharmaceutical development
A satisfactory account of the pharmaceutical development has been provided.

In line with the Draft guideline on quality and equivalence of topical products (CHMP/QWP/708282/2018), extended pharmaceutical equivalence (in terms of similarity of pharmaceutical form, qualitative and quantitative composition, microstructure/physical properties, product performance and method of administration) between the test and reference products has been demonstrated.

Product performance was evaluated by *in vitro* release testing (IVRT) studies along with *in vitro* skin permeation and penetration testing (IVPT) and *in vitro* antibacterial activity studies (discussed in section IV).

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

No excipients of animal or human origin are used in the finished product.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product
A description and flow-chart of the manufacturing method has been provided.

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specification
The finished product specification is satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 24 months, with the storage conditions "Store in a refrigerator (2ºC to 8ºC). Do not freeze" is acceptable.

The shelf life of the medicinal product after dispensing is 2 months, with the storage conditions of "Do not store above 25ºC".

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a marketing authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of clindamycin and benzoyl peroxide are well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

III.2 Pharmacology
No new pharmacology data were provided and none were required for this application.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided and none were required for this application.

III.4 Toxicology
No new toxicology data were provided and none were required for this application.

III.5 Ecotoxicity/Environmental Risk Assessment
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As this is a hybrid application of an already authorised product, it is not expected that environmental exposure will increase following approval of the Marketing Authorisation for the proposed product.

III.6 Discussion on the non-clinical aspects
The grant of a marketing authorisation is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction
In accordance with the regulatory requirements, the applicant has provided a suitable

biowaiver. No clinical bioequivalence or therapeutic equivalence studies have been submitted with this application.

To support the biowaiver the applicant has provided extended pharmaceutical equivalence data including IVRT data, an IVPT study and an *in vitro* skin infection study.

IV. 2 Pharmacokinetics

No new pharmacokinetic data have been submitted for this application and none were required.

IV.3 Pharmacodynamics

No new pharmacodynamic data have been submitted for this application and none were required.

IV.4 Clinical efficacy

In support of the application, the applicant submitted the following *in vitro* studies.

- Comparative evaluation of in vitro release of Clindamycin from gel formulations
- Comparative evaluation of *in vitro* release of Benzoyl peroxide from gel formulations
- Comparative evaluation of *in vitro* penetration and permeation (proxy for absorption) of Clindamycin and Benzoyl peroxide in human skin from gel formulations
- Comparative evaluation of *in vitro* antibacterial activity of Clindamycin and Benzoyl Peroxide

Study 1

IVRT study: Comparative evaluation of *in vitro* release of clindamycin from gel formulations

To support extended pharmaceutical equivalence, an *in vitro* release study on Franz cells was performed on three batches of test product, Clindamycin + Benzoyl Peroxide 10 mg/g + 50 mg/g Gel, and three batches of reference product, Duac Once Daily 10mg/g + 50mg/g Gel.

The study measured the release of the active substance clindamycin, from vehicle, across a synthetic membrane.

The study was conducted in accordance with the Food and Drug administration (FDA) Nonsterile Semisolid Dosage Forms; Scale-Up and Post-Approval Changes (SUPAC-SS) guidance and the United States Pharmacopeia (USP) General Chapter 1724.

A summary of the results is presented below:

Results for the release of clindamycin for the reference product and test product

	Slope after 3 h [µg·cm^{-2}·h$^{-0.5}$]		Transported amount after 3 h [µg·cm^{-2}]		Amount released after 3 h [%]
	Mean	CV [%]	Mean	CV [%]	
Reference	516.79	8.70	794.94	6.95	48.75
Test	457.21	6.54	729.64	6.23	48.67
Reference	439.24	8.29	693.15	6.85	44.63
Test	430.67	13.10	693.19	10.90	45.66
Reference	461.39	9.66	761.40	9.23	51.69
Test	441.87	5.33	716.67	3.74	47.04
Reference	479.25	9.08	785.81	6.20	49.01
Test	459.18	7.89	768.45	5.92	48.10
Reference	462.85	17.19	767.68	16.89	46.85
Test	410.78	12.03	692.87	11.32	47.27
Reference	510.04	6.15	798.12	5.65	51.95
Test	466.65	9.58	729.60	8.83	49.96
Reference	457.68	7.11	709.71	7.04	45.21
Test	470.02	3.45	740.37	3.52	46.39
Reference	428.93	6.77	697.10	7.50	44.06
Test	407.92	10.23	661.86	10.35	42.96
Reference	445.62	9.54	742.15	8.21	50.07
Test	435.38	12.19	718.38	11.90	44.80

Statistical comparison of test product and reference product

Values of the 90 % confidence interval		
8th value	29th value	Significant difference
0.81	0.96	No
0.85	1.15	No
0.87	1.06	No
0.87	1.05	No
0.76	1.08	No
0.83	0.98	No
0.98	1.10	No
0.85	1.04	No
0.90	1.15	No

Conclusion

There is no statistically significant difference in the release rate between the three reference batches and the three test batches. The lower limit of the 90 % confidence interval is 0.75 and the upper limit is 1.33. For all performed IVRT experiments both values are within the range of the lower and upper limit (8th value of T/R ratios in range: 0.76 and 0.98, 29th value of T/R ratios in range: 0.96 and 1.15 i.e. 8th value of T/R ratios in range 76% and 98%, 29th

value of ratios in range: 96% and 115%). Therefore, the formulations are statistically not different according the SUPAC-SS guideline.

The *in vitro* release rate of clindamycin from test product is comparable with the reference product.

Study 2
IVRT study: Comparative evaluation of in vitro release of benzoyl peroxide from gel formulations

To support extended pharmaceutical equivalence, an *in vitro* release study on Franz cells was performed on three batches of test product, Clindamycin + Benzoyl Peroxide 10 mg/g + 50 mg/g Gel, and three batches of reference product, Duac Once Daily 10mg/g + 50mg/g Gel.

The study measured the release of the active substance benzoyl peroxide, from vehicle, across a synthetic membrane.

The study was conducted in accordance with the Food and Drug administration (FDA) Nonsterile Semisolid Dosage Forms; Scale-Up and Post-Approval Changes (SUPAC-SS) guidance and the United States Pharmacopeia (USP) General Chapter 1724.

A summary of the results is presented below:

Results for the release of benzoyl peroxide

	Slope after 5 h [$\mu g \cdot cm^{-2} \cdot h^{-0.5}$]		Transported amount after 5 h [$\mu g \cdot cm^{-2}$]		Amount released after 5h [%]
	Mean	CV [%]	Mean	CV [%]	
Reference	1192.94	10.86	2229.29	6.75	28.15
Test	1324.45	13.18	2289.38	16.81	28.47
Reference	1306.44	23.53	2353.78	9.69	29.57
Test	1248.19	15.55	2332.40	12.63	29.01
Reference	1223.14	9.14	2455.69	7.95	31.43
Test	1106.41	12.82	2103.16	13.96	26.20
Reference	1363.51	11.39	2442.86	10.04	29.86
Test	1365.07	17.71	2459.28	15.05	33.19
Reference	1171.53	7.10	2149.31	6.84	29.66
Test	1197.40	11.98	2222.42	10.71	31.73
Reference	1189.00	11.57	2302.09	11.12	29.86
Test	1372.00	10.62	2595.34	9.28	34.80
Reference	1043.47	13.27	1913.17	10.78	24.28
Test	1186.40	10.07	2137.28	9.21	27.69
Reference	1141.19	12.62	2074.71	10.53	27.08
Test	1135.69	6.12	2032.67	6.00	27.88
Reference	1142.88	9.19	2105.48	7.55	27.43
Test	1196.48	8.21	2146.82	8.55	28.04

Statistical comparison of test product and reference product

Values of the 90 % confidence interval		
8th value	29th value	Significant difference
0.96	1.31	No
0.78	1.17	No
0.79	1.04	No
0.82	1.20	No
0.89	1.15	No
1.01	1.35	Yes
0.97	1.26	No
0.92	1.11	No
0.96	1.17	No

Not all experimental results exhibited no significant difference. The experiment performed in run 6 did not pass at the first stage of the release test, therefore, according to SUPAC-SS, USP General Chapter 1724 and the study protocol, the second stage of release test was carried out.

Results for the release of benzoyl peroxide for the second stage

	Slope after 5 h [$\mu g \cdot cm^{-2} \cdot h^{-0.5}$]		Transported amount after 5 h [$\mu g \cdot cm^{-2}$]		Amount released after 5 h [%]
	Mean	CV [%]	Mean	CV [%]	
Reference	1414.62	10.83	2611.97	10.00	33.72
Test	1533.10	10.88	2838.56	10.22	37.91

Statistical comparison of test product and reference product – second stage

Values of the 90 % confidence interval		
110th value	215th value	Significant difference
0.99	1.18	No

Conclusion

There is no statistically significant difference in the release rate between the three reference batches and the three test batches. The lower limit of the 90 % confidence interval is 0.75 and the upper limit is 1.33. For all performed IVRT experiments (except for one) both values are within the range of the lower and upper limit (8th value of T/R ratios in range: 0.78 and 0.97, 29th value of T/R ratios in range: 1.04 and 1.31 i.e. 8th value of T/R ratios in range 78 % and 97 %, 29th value of ratios in range: 104 % and 131 %). Therefore, the formulations are statistically not different according the SUPAC-SS guideline and USP General Chapter 1724 and it is confirmed that the *in vitro* release rate of benzoyl peroxide from test product is comparable with the reference product.

For the experiment performed in run 6, the 29th value amounted to 1.35 which was not within the limit of 1.33 leading to the performance of a second stage experiment (12 additional Franz cell per test item were investigated). The results of the second stage experiment indicated no statistically significant difference between the reference and test product (110th value: 0.99 and 215th value: 1.18), therefore the *in vitro* release rate of

benzoyl peroxide from test product is also comparable with the reference product.

Study 3
IVPT study: *In vitro* permeation/penetration in the human skin

This study was conducted to compare the permeation and penetration of the test and reference clindamycin/benzoyl peroxide gels in excised human donor skin samples. The method was developed, validated and documented in line with the EMA Draft guideline on quality and equivalence of topical products (CHMP/QWP/708282/2018). Bioanalytical methods were validated in line with the respective guideline. Skin samples (punction) were obtained from 12 healthy subjects (abdominal skin) and all samples were processed in duplicate.

The positive control was a 50% clindamycin/benzoyl peroxide gel and the negative control was placebo (vehicle). One batch of test and reference product were tested.

For the permeation study, over 48 hours clindamycin phosphate was detected in only sporadic acceptor samples and was mostly below the lower level of quantification (LLOQ). Mass balance analysis demonstrated practically 100% and 97% recovery of the applied amount on the application side. Expectedly, benzoyl peroxide was not detected in any acceptor samples, as absorption of benzoyl peroxide through the skin can only occur following its conversion to benzoic acid. Benzoic acid was detected in some acceptor samples but was mostly below the LLOQ. Hence, calculation (and comparison) of the preferred indices – total amount permeated (Atotal) and maximal rate of absorption (Jmax) was not possible. Test and Reference samples behaved identically in that there was practically no permeation, which is in line with expectations.

After completion of the permeation part, skin samples were cut into slices of dermis and epidermis to analyse the presence of clindamycin, benzoyl peroxide and benzoic acid. Most dermis samples yielded concentrations below the LLOQ for all analytes. Even when set at half of the LLOQ, amounts detected in combined epidermis and dermis were around 0.16% to 0.34% of the applied dose of clindamycin and around 0.17% to 0.40% of applied dose of benzoyl peroxide. Minute concentrations of benzoic acid were also detected. Using the Mann-Whitney U-test, no statistically significant difference between test and reference products was detected regarding skin concentrations of clindamycin, benzoyl peroxide or benzoic acid. As in the case of permeation, the test and reference product behaved identically in that only minute amounts of active ingredients were detected in the skin and practically 100% recovery of the applied amount from the surface of the samples was obtained.

Conclusion
The mechanism of action of Clindamycin + Benzoyl Peroxide 10 mg/g + 50 mg/g Gel is said to take place on the surface and upper layers of the skin. There was no significant difference between the test and reference products in terms of permeation/penetration. The study provides supportive data.

Study 4
***In vitro* comparative antimicrobial effect study**

The skin disc antibiogram model was used. Skin samples from 12 healthy donors were obtained, stratum corneum (the main barrier for drug permeation) was removed by stripping technique, and epidermis/dermis was cut into 300 µm slices. From each slice, samples 13 µm in diameter were obtained. Sterilized skin samples were dosed with 50

µL (µg) of Test product, Reference product, positive control for clindamycin (100% clindamycin gel), positive control for benzoyl peroxide (100% BPO gel) and a negative control (placebo-vehicle) and placed on anaerobe standard Agar with *P. acnes*. Samples from each donor (n=12) were analysed twice, i.e., separately by two operators (n=24 processed samples – for each test item). Finally, each of the 24
processed samples per test item was actually a set of 6 13 µm skin samples. Therefore, test and reference were each evaluated in 144 runs (12 donors x 2 operators x 6 skin samples). The outcome of interest was inhibition zone diameter indicating activity of the applied product against *P. acnes* after permeation through human epidermis/dermis.

The method was developed, validated and documented in line with the EMA Draft guideline on quality and equivalence of topical products (CHMP/QWP/708282/2018).
The results were consistent across two operators and were analysed jointly.

The results are summarised below:

Variable	N	Mean	-90% CI	+90% CI	Min	Max	SD
Reference/Test	144	0.910	0.867	0.952	0.333	1.762	0.305

Conclusion
The 90% confidence interval of the ratios is 0.867 to 0.952 which is within the limits of 0.8 to 1.25 and exhibits no statistically significant difference. In was concluded that there was no statistical difference between test and reference product in terms of antibacterial activity.

Overall conclusion on therapeutic equivalence
Overall, extended pharmaceutical equivalence has been demonstrated. The similarity with respect to quality should be taken into consideration when considering the *in-vitro* permeation data. The IVRT results look similar and the applicant has demonstrated compliance with SUPAC-SS. The skin permeation studies are also supportive. Acceptable *in-vitro* data supporting equivalence has been provided.

IV.5 Clinical safety
No new safety data were submitted with this application and none were required. The safety profile for this product is considered to be the same as Duac Once Daily 10mg/g + 50mg/g Gel.

IV.6 Risk Management Plan (RMP)
The applicant has submitted an RMP, in accordance with the requirements of Directive 2001/83/EC, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects
The grant of a marketing authorisation is recommended for this application.

V USER CONSULTATION

A user consultation with target patient groups on the Patient Information Leaflet (PIL) has been performed on the basis of a bridging report making reference to Clindamycin + Benzoyl Peroxide 10 mg/g + 50 mg/g Gel (PL 35533/0035; Aspire Pharma Limited). The bridging report submitted by the applicant is acceptable.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified.

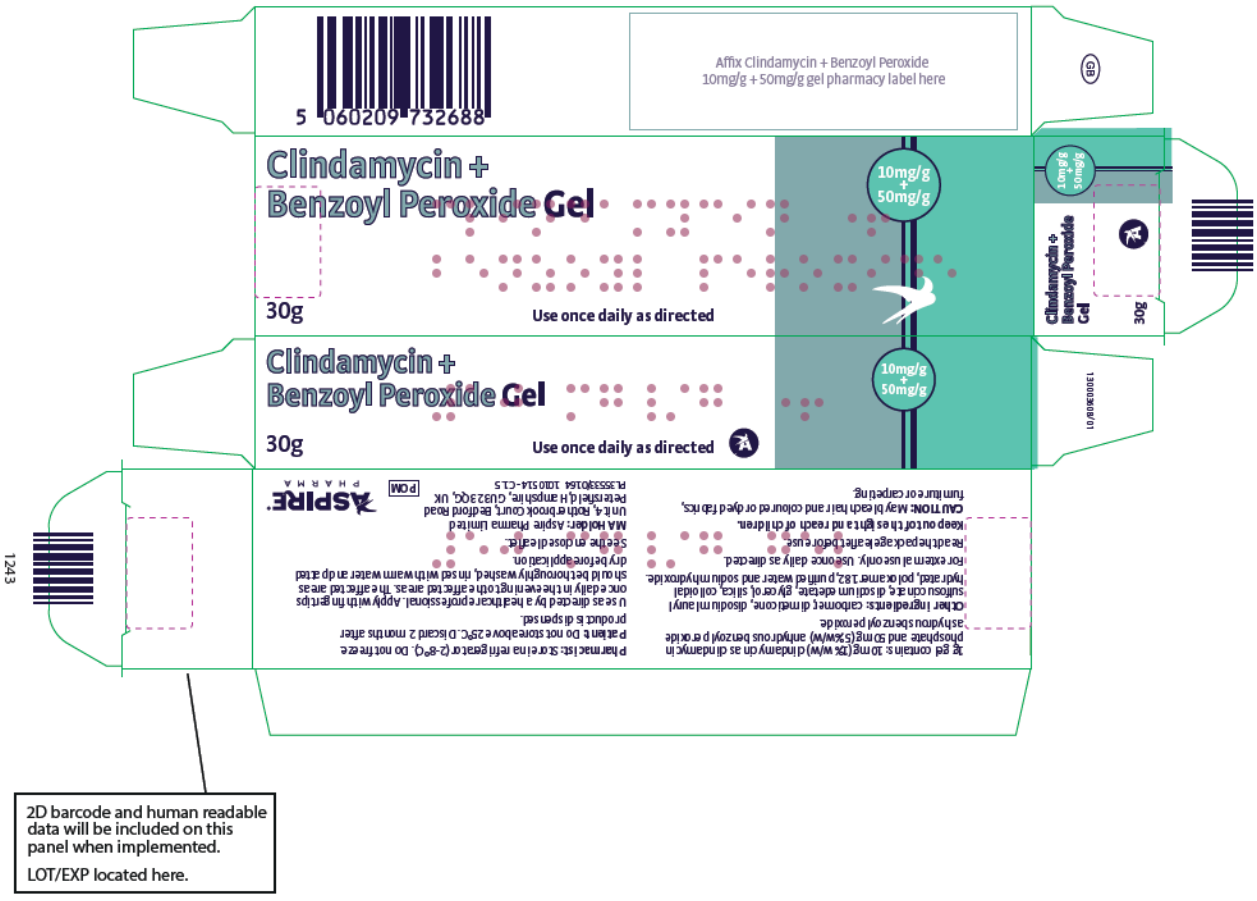
Extensive clinical experience with clindamycin and benzoyl peroxide is considered to have demonstrated the therapeutic value of the product.

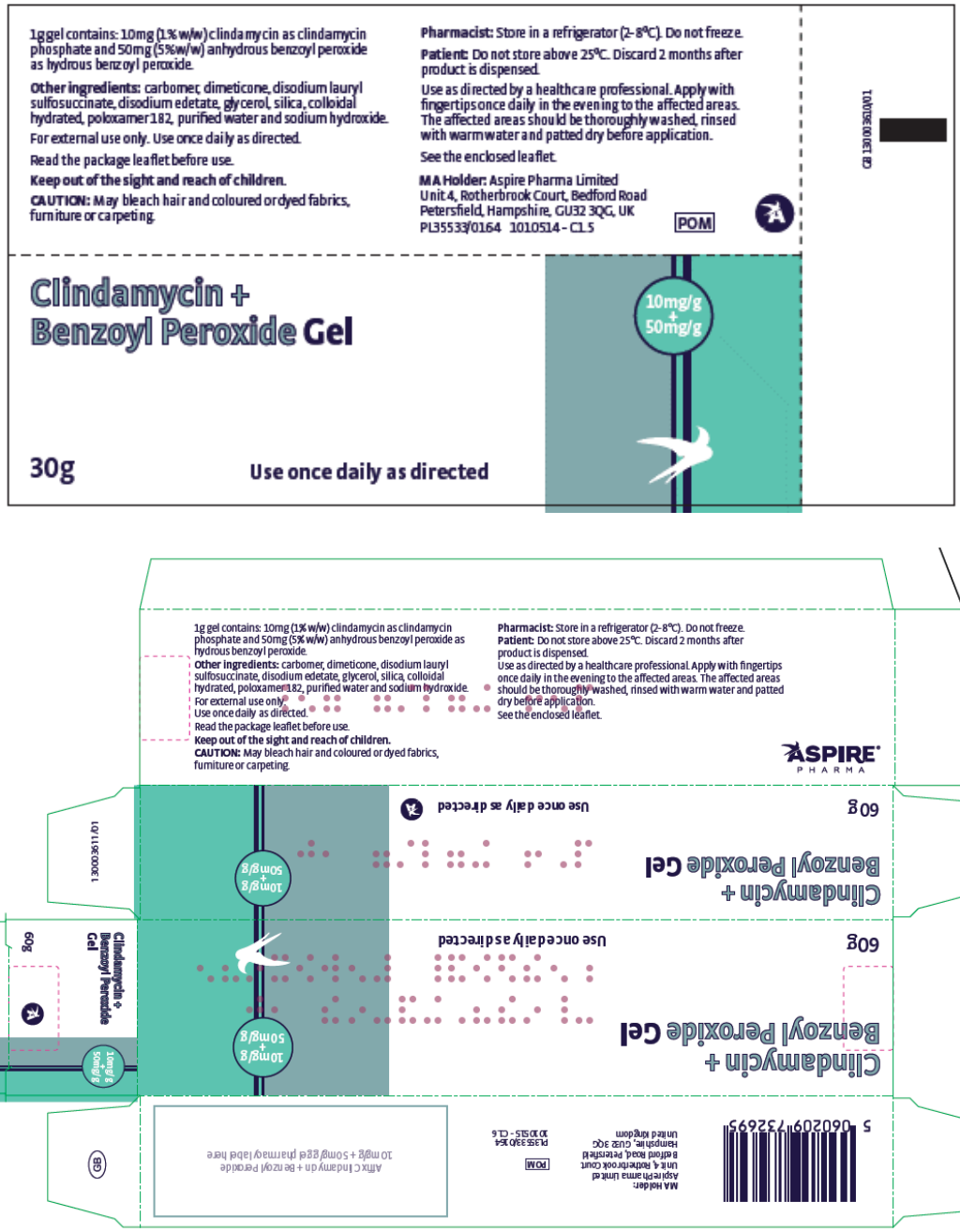
The benefit/risk is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory and in line with current guidelines.

In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPCs and PILs for these products are available on the MHRA website.

Representative copies of the labels at the time of UK licensing are provided below.




1g gel contains: 10mg (1% w/w) clindamycin as clindamycin phosphate and 50mg (5% w/w) anhydrous benzoyl peroxide as hydrous benzoyl peroxide.
Other ingredients: carbomer, dimeticone, disodium lauryl sulfosuccinate, disodium edetate, glycerol, silica, colloidal hydrated, poloxamer 182, purified water and sodium hydroxide.
For external use only. Use once daily as directed.
Read the package leaflet before use.
Keep out of the sight and reach of children.
CAUTION: May bleach hair and coloured or dyed fabrics, furniture or carpeting.
Pharmacist: Store in a refrigerator (2-8°C). Do not freeze.
Patient: Do not store above 25°C. Discard 2 months after product is dispensed.
Use as directed by a healthcare professional. Apply with fingertips once daily in the evening to the affected areas. The affected areas should be thoroughly washed, rinsed with warm water and patted dry before application.
See the enclosed leaflet.
MA Holder: Aspire Pharma Limited
Unit 4, Rotherbrook Court, Bedford Road
Petersfield, Hampshire, GU32 3QG, UK
PL35533/0164 1010514 - C1.5
POM
Clindamycin + Benzoyl Peroxide Gel
10mg/g + 50mg/g
30g
Use once daily as directed

1g gel contains: 10mg (1% w/w) clindamycin as clindamycin phosphate and 50mg (5% w/w) anhydrous benzoyl peroxide as hydrous benzoyl peroxide.
Other ingredients: carbomer, dimeticone, disodium lauryl sulfosuccinate, disodium edetate, glycerol, silica, colloidal hydrated, poloxamer 182, purified water and sodium hydroxide.
For external use only.
Use once daily as directed.
Read the package leaflet before use.
Keep out of the sight and reach of children.
CAUTION: May bleach hair and coloured or dyed fabrics, furniture or carpeting.
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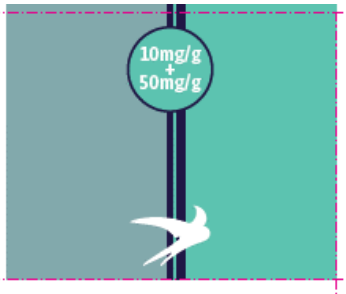
See the enclosed leaflet.
ASPIRE PHARMA
60g
Use once daily as directed
Clindamycin + Benzoyl Peroxide Gel
10mg/g + 50mg/g
GB
POM
PL35533/0164
30.05.15 - C1.6
MA Holder:
Aspire Pharma Limited
Unit 4, Rotherbrook Court
Bedford Road, Petersfield
Hampshire, GU32 3QG
United Kingdom
5 060209 732695
1300361101
1244

Clindamycin + Benzoyl Peroxide Gel



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MA Holder: Aspire Pharma Limited
Unit 4, Rotherbrook Court, Bedford Road
Petersfield, Hampshire, GU32 3QG, UK

POM

PL35533/0164
1010515 - CL7

GB 13000001 TAE

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 SmPC and/or PIL available on the MHRA website.

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