Public Assessment Report

Decentralised Procedure

Duac Once Daily 10 mg/g + 30 mg/g Gel

Clindamycin phosphate
Hydrous benzoyl peroxide

Procedure No: UK/H/0676/002/DC

UK licence no: PL 19494/0251

Glaxosmithkline UK Limited
Duac Once Daily 10 mg/g + 30 mg/g Gel

PL 19494/0251

LAY SUMMARY

On 27th March 2013, the Medicines and Healthcare products Regulatory Agency (MHRA) granted a Marketing Authorisation to Glaxosmithkline UK Limited for the medicinal product Duac Once Daily 10 mg/g + 30 mg/g Gel (PL 19494/0251; UK/H/0676/02/DC). This is a prescription-only medicine (POM).

DUAC ONCE DAILY GEL contains two medicines: clindamycin and benzoyl peroxide. DUAC ONCE DAILY GEL belongs to a group of medicines known as ‘anti-acne preparations’.

DUAC ONCE DAILY GEL is used for treating mild to moderate acne on your skin.

- 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.

Used together in DUAC ONCE DAILY GEL, these work by:

- fighting the bacteria that can cause acne
- treating existing blackheads, whiteheads, and spots
- lowering the number of red, inflamed acne spots

DUAC ONCE DAILY GEL is for use by adults and adolescents aged twelve years or over.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of treatment with Duac Once Daily 10 mg/g + 30 mg/g Gel outweigh the risks, hence a Marketing Authorisation has been granted.
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# Module 1

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<th>Product Name</th>
<th>Duac Once Daily 10 mg/g + 30 mg/g Gel</th>
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<tr>
<td>Type of Application</td>
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<td>980 Great West Road</td>
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Module 2
Summary of Product Characteristics

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.
Module 3
Patient Information Leaflet

In accordance with Directive 2010/84/EU the Patient Information Leaflets (PIL) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.
Module 4

Labelling
Duac®
Once Daily
10 mg/g + 30 mg/g Gel
clindamycin + anhydrous benzoyl peroxide

Active Ingredients: 1 g gel contains: 10 mg (1% w/w) clindamycin as clindamycin phosphate and 30 mg (3% w/w) anhydrous benzoyl peroxide as hydrogen peroxide.

Other ingredients: carboxymethyl cellulose, dibutylphthalate, dioctyl sebacate, glycerol, silicate (sodium type), poloxamer 182, purified water, sodium hydroxide.

Keep out of the sight and reach of children. Read the package leaflet before use.

Storage:
Do not store above 25°C. Discard 2 months after opening.

Stiefel

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Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMSs) consider that the application for Duac Once Daily 10 mg/g + 30 mg/g Gel for the topical treatment of mild to moderate acne vulgaris, particularly inflammatory lesions, in adults and adolescents aged 12 years and above, could be approved.

This decentralised application has been submitted under article 10(b), fixed combination application. The proposed product Duac Once Daily 10 mg/g + 30 mg/g Gel represents a line extension to the currently marketed higher strength Duac Once Daily 10 mg/g + 50 mg/g Gel (PL 00174/0217), first authorised to Stiefel Laboratories (UK) Limited on 17th September 2003. This application then underwent a change of ownership procedure to the Marketing Authorisation holder Glaxosmithkline UK Limited (PL 19494/0075) on 19th January 2011.

The proposed line extension (Duac Once Daily 10 mg/g + 30 mg/g Gel) contains the same drug substances as the licensed drug product, using a lower concentration of benzoyl peroxide and the concentrations of 2 excipients (dimethicone, an emollient, and glycerine, a humectant) have been increased.

With UK as the RMS in this Decentralised Procedure (UK/H/0676/002/DC), GlaxoSmithKline UK Limited applied for the Marketing Authorisation for Duac Once Daily 10 mg/g + 30 mg/g Gel in the following CMSs:

UK/H/0676/002/DC: Bulgaria, Cyprus, Czech Republic, Germany, Greece, Italy, Latvia, Lithuania, Malta, Poland, Republic of Ireland, Romania, Slovenia and Spain.

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.

Although clindamycin phosphate is inactive in-vitro, rapid in-vivo hydrolysis converts this compound to the antibacterial active clindamycin. Clindamycin activity has been demonstrated clinically in comedones from acne patients at sufficient levels to be active against most strains of Propionibacterium acnes. Clindamycin in-vitro inhibits all Propionibacterium acnes cultures tested (MIC 0.4 mcg/ml). Free fatty acids on the skin surface have been decreased from approximately 14 % to 2 % following application of clindamycin.

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.

No new non-clinical studies were conducted, which is acceptable given that the application was based on being a line extension of an existing medicinal product. The in vivo irritation
study and *in vitro* skin penetration study were carried out.

To support the application, the Marketing Authorisation Holder submitted two clinical studies (W0261-101 and W0261-301). These studies were carried out to determine if the bioavailability of clindamycin and its metabolite clindamycin sulfoxide are altered by the concentration of BPO or the changes in the vehicle and to evaluate the safety and efficacy of CLN 1%-BPO 3% relative to its individual active constituents and to its vehicle in the treatment of acne when applied once daily for 12 weeks. The studies were carried out in accordance with Good Clinical Practice (GCP).

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

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

All member states agreed to grant a respective Marketing Authorisation for the above product at the end of procedure (Day 210 – 4th March 2013). After a subsequent national phase, the UK granted a Marketing Authorisation for this product on 27th March 2013 (PL 19494/0251).
## II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Duac Once Daily 10 mg/g + 30 mg/g Gel</th>
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<tr>
<td>Name(s) of the active substance(s) (USAN)</td>
<td>Clindamycin Phosphate, Hydrous Benzoyl Peroxide</td>
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<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Clindamycin, combinations, ATC Code: D10AF51</td>
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<td>Gel, 10 mg/g + 30 mg/g</td>
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<td>Reference Member State</td>
<td>United Kingdom</td>
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<td>Marketing Authorisation Number(s)</td>
<td>PL 19494/0251</td>
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<tr>
<td>Name and address of the authorisation holder</td>
<td>GlaxoSmithKline UK Limited, 980 Great West Road, Brentford, Middlesex, TW8 9GS</td>
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III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

DRUG SUBSTANCE

INN: Clindamycin phosphate
Chemical name: Methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl-trans-4-propyl-L-2-pyrrolidinocarboxamido)-1-thio-L-threo-a-D-galacto-octopyranoside 2-(dihydrogen phosphate)

Structure:

![Clindamycin phosphate structure]

Molecular formula: C_{18}H_{34}ClN_{2}O_{8}PS
Molecular weight: 504.97
Physical form: White to almost white, slightly hygroscopic powder
Solubility: It is freely soluble in water, slightly soluble in dehydrated alcohol, very slightly soluble in acetone and practically insoluble in chloroform, benzene, and ether.

Clindamycin phosphate is the subject of a European Pharmacopoeia monograph.

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

INN: Hydrous Benzoyl Peroxide
Chemical name: Dibenzoyl Peroxide
Structure:

![Dibenzoyl Peroxide structure]

Molecular formula: C_{14}H_{10}O_{4}
Molecular weight: 242.2
Physical form: a white, hygroscopic powder.
Solubility: It is insoluble in water, slightly soluble in alcohol and soluble in acetone or dichloromethane.

Hydrous Benzoyl Peroxide is the subject of a European Drug Master File (EDMF).

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the drug substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Certificate of Analysis for all working standards have been provided.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory specifications and certificates of analysis have been provided for all packaging used to store the drug substance. Confirmation has been provided that the primary packaging complies with current guidelines concerning materials in contact with food.

Appropriate stability data have been generated, supporting a suitable retest period when the drug substance is stored in the packaging proposed.

**DRUG PRODUCT**

**Other Ingredients**

Other ingredients consist of the pharmaceutical excipients carbomer, dimethicone, disodium lauryl sulfosuccinate, disodium edetate, glycerol, silica, dental type, poloxamer 182, sodium hydroxide and purified water.

All excipients comply with the European Pharmacopoeia monograph with the exception of poloxamer 182 and disodium lauryl sulfosuccinate which are covered by an in-house specification. Satisfactory Certificates of Analysis have been provided for these excipients.

The above excipients do not contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of this product.

There were no novel excipients used.

**Pharmaceutical Development**

The objective of the pharmaceutical development programme was to obtain stable topical preparation that was therapeutically equivalent to the currently marketed Duac topical gel (clindamycin 1% - benzoyl peroxide 5%; “Duac”) with reduced cutaneous irritation reactions.

Suitable pharmaceutical development data have been provided for this application.

Comparative skin penetration study, rheology study and impurity profiles have been provided for the proposed and originator products.

**Manufacture**

Satisfactory batch formulae have 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. The applicant has committed to perform process validation on future commercial-scale batches.

**Finished Product Specifications**

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

**Container Closure System**

The finished product is supplied in linear low density polyethylene (LLDPE) tube with polypropylene screw cap with a flip up lid with a pack size of 30 grams.

Specifications and Certificates of Analysis for the primary packaging material have been provided. These are satisfactory. All primary packaging is controlled to European Pharmacopoeia standards and complies with guidelines.

**Stability**

Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, shelf-lives of 24 months as packaged for sale and 2 months after dispensing are set. These are satisfactory.

The proposed storage conditions prior to dispensing are “Store in a refrigerator (2°C-8°C)” and “Do not freeze” and after dispensing is “Do not store above 25°C”. These are satisfactory.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling**

The SPC, PIL and labelling are pharmaceutically satisfactory.

User testing of the package leaflet has been accepted, based on a bridging report provided by the applicant making reference to the user-testing of the PIL for Duac Once Daily Gel (10 mg/g + 50 mg/g). The products are from the same therapeutic class and have similar indications. A critical analysis demonstrated that the key messages for safe and effective use for both leaflets were similar. The justification of the rationale for bridging is accepted.

**Marketing Authorisation Application (MAA) Forms**

The MAA form is pharmaceutically satisfactory.

**Expert Report**

A pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

**Conclusion**

There are no objections to the approval of this product from a pharmaceutical point of view.

**III.2  NON-CLINICAL ASPECTS**

**PHARMACODYNAMICS, PHARMACOKINETICS, TOXICOLOGY**

The pharmacological, pharmacokinetic and toxicological properties of clindamycin phosphate and hydrous benzoyl peroxide are well-known.
No new non-clinical pharmacology studies were conducted which is acceptable. Non-clinical pharmacokinetics (in vitro skin permeation) and toxicology (in vivo ocular irritation) bridging studies have been conducted. Whilst there are limitations to both studies, the ocular tolerance test showed the potential for minimal irritation with both Duac LD Once Daily Gel and Duac Topical Gel® with no new findings and the non-GLP in vitro study suggested that delivery of the licensed product compared to Duac LD Once Daily Gel is similar for clindamycin and as expected for benzoic acid.

The non-clinical sections (4.6 and 5.3) of the SmPC are in line with the licensed Duac Gel product and are acceptable.

The non-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

Satisfactory environmental risk assessment (ERA) has been provided.

There are no objections to the approval of this product from a non-clinical point of view.

III.3 CLINICAL ASPECTS

The applicant has developed clindamycin 1%-benzoyl peroxide 3% gel (CLN 1%-BPO 3%) for the topical treatment of mild-to-moderate acne vulgaris, particularly inflammatory lesions, in patients 12 years of age and older. The proposed product, Duac Once Daily 10 mg/g+30 mg/g Gel, is referred to as Duac LD gel in this report.

The application is supported by:

1. Study W0261-101: to determine if the bioavailability of clindamycin and its metabolite clindamycin sulfoxide are altered by the concentration of BPO or the changes in the vehicle. This study assessed systemic exposure under maximal-use conditions. Subjects with moderate-to-severe acne applied 4 grams of study product to the face, upper chest, upper back, and shoulders once daily for 5 days. The following clindamycin-BPO combination product formulations were evaluated:
   • CLN 1%-BPO 3% Gel (clindamycin 1%-BPO 3%), methylparaben-free.
   • Duac Topical Gel (clindamycin 1%-BPO 5%), methylparaben-preserved (Duac-MP); formulation that is currently marketed in the US.
   • Duac Once Daily Gel (clindamycin 1%-BPO 5%), methylparaben-free (Duac-MPF); formulation that is currently marketed in Europe.

2. Study W0261-301: a large (N=1315 subjects), multicentre, randomised, double-blind, parallel-group, active- and vehicle-controlled study intended to evaluate the safety and efficacy of CLN 1%-BPO 3% relative to its individual active constituents and to its vehicle in the treatment of acne when applied once daily for 12 weeks.

3. Previous clinical studies of the Duac (1% clindamycin +5% BPO) once daily gel

According to Committee for Proprietary Medicinal Products (CPMP) guidelines on minimum clinical requirements for a different strength of a topical formulation [CPMP/EWP/239/95 Final], a dossier should include pharmacodynamic studies or local availability studies and possibly in vitro studies. In addition to these minimum requirements, Stiefel performed a full phase 3 study, which was in line with the CPMP Points to Consider document [CPMP/EWP/2330/99] describing considerations for using a single pivotal study for phase 3 clinical development. The fundamental requirements include adequate and well-controlled data of good quality, demonstrating a positive benefit/risk in the intended population at the intended dose and manner of use.
Pharmacokinetics (In-Vivo Relative Bioavailability Study) – STUDY W0261-101

A phase 1, single centre, randomised, open-label study to evaluate the bioavailability of Clindamycin from Clindamycin 1%-Benzoyl Peroxide 3% Gel, Duac Topical Gel (Clindamycin 1%-Benzoyl Peroxide 5%), and Duac LD Once Daily Gel (Clindamycin 1%-Benzoyl Peroxide 5%) in Subjects with Acne Vulgaris.

Study Design:
This was a single-centre, randomised, open-label, parallel-group, active-controlled, relative bioavailability study that was conducted under maximal-use conditions in 72 male and female subjects, 12 to 45 years of age, who had moderate-to-severe acne (based on an Investigator’s Static Global Assessment [ISGA] score of 3 or greater at baseline).

The study consisted of a 5-day dosing period during which subjects applied 4 grams of study product to the face, upper chest, upper back, and shoulders, once daily in the morning, while at the study center. Study visits were scheduled every day for 6 days. Plasma concentrations of clindamycin and its metabolite clindamycin sulfoxide were determined from blood samples collected at baseline/day 1; on day 2, day 3, and day 4 before study product applications; on day 5 before study product application and at 1, 2, 4, 6, 8, and 12 hours (±10 minutes) after application; and on day 6 at 24 hours (±1 hour) after the last study product application. Concentrations of clindamycin and clindamycin sulfoxide in human plasma were determined using a validated bioanalytical method with a linear range of quantification for clindamycin (free base) and clindamycin sulfoxide concentrations in human plasma of 50 to 20,000 pg/mL.

The pharmacokinetic parameters that were calculated were – C_{max}, T_{max}, AUC_{0-1}, AUC_{0-infinity} and t_{1/2}.

The objective of this study was to compare the bioavailability of clindamycin after application of the proposed Duac LD gel formulation with that of currently licensed higher strength Duac gel formulations. The use of a maximal-use conditions where each subject applied 4 grams of gel each day for 5 days is appropriate. The use of 4 grams and the duration of 5 days have been supported by previous published studies. The use of multiple doses is also appropriate to take in to consideration possible accumulation effects.

The applicant did not measure BPO levels in this study for the following reasons:

“Topical application of BPO has a low potential for systemic toxicity, and the US FDA considers BPO 2.5% to 10% to be a ‘generally recognized as safe and effective’ active ingredient in non-prescription topical acne products. Further, the transepidermal delivery of BPO has been shown to be concentration-dependent; thus, the systemic exposure to BPO and benzoic acid from CLN 1%-BPO 3% would be lower than exposure from Duac. Due to the limited utility, plasma concentrations of BPO or benzoic acid were not assessed during study W0261-101.”

Taking in to consideration that the proposed formulation has a lower strength of BPO than the currently licensed formulation of Duac gel and the fact that the main objective of this relative bioavailability study is to compare systemic exposures as a surrogate for systemic safety, it is accepted not to measure BPO as 3% BPO is likely to be at least as safe as 5% BPO. This is especially true as it is noted that different formulations of topical BPO with strengths up to 10% is currently approved. As 1% Clindamycin was used in both Duac formulations, this study proposed to evaluate the systemic exposure of clindamycin to
conclude if changes in formulation affected absorption of clindamycin. This study evaluated both the parent –clindamycin and metabolite clindamycin sulfoxide.

The study report indicates that the study was conducted in compliance to ICH-GCP.

**Results:**
Mean plasma concentrations of clindamycin increased slowly, reaching maximal observed concentrations within 4 to 8 hours after topical application on day 5 for all 3 formulations (see Figure 1 and Table 2). The highest individual plasma concentration on day 5 was in the Duac-MP group (5090 pg/mL at 8 hours postdose), followed by the CLN 1%-BPO 3% group (4140 pg/mL at 2 hours postdose) and Duac-MPF group (3560 pg/mL at 12 hours postdose).

**Figure 1:** Clindamycin Day 5 Plasma Concentration versus Time - Linear Scale (Pharmacokinetic Analysis Set) – Study W0261-101

Source: Figure 1.1, Section 14.2 of the W0261-101 CSR (m5.3.1.1).

Note: Samples with concentrations below the limit of quantification were set to missing.
The mean terminal t1/2 for clindamycin was approximately 10 hours and was comparable across all 3 formulations. Of note, the calculated terminal t1/2 for few subjects was greater than the sample collection time of 24 hours. Therefore, the t1/2 values in these subjects should be viewed with caution.
Safety:
Overall, 5 subjects experienced at least 1 adverse event (AE) during the study: 3 subjects (nausea, vomiting and headache) in the CLN 1%–BPO 3% group, 1 subject (nasopharyngitis) in the Duac–MP group, and 1 subject (Joint sprain) in the Duac–MPF group. None of the AEs were considered by the investigator to be related to study product. There were no severe AEs, severe treatment-related AEs, AEs leading to discontinuation, or SAEs. There were no clinically significant changes in vital signs during the study. Topical application of CLN 1%–BPO 3%, Duac–MP, or Duac–MPF under maximal-use conditions for 5 days appeared to be safe and well tolerated.

Pharmacokinetic conclusions
Clindamycin was slowly absorbed after topical application, reaching maximal observed plasma concentrations within 4 to 8 hours on Day 5 for all 3 formulations. Mean (±SD) maximal plasma exposure (C\text{max}) was highest in the Duac–MP group (1426.0 ±1072.73 pg/mL), followed by the CLN 1%–BPO 3% group (1294.2 ±1011.31 pg/mL) and Duac–MPF group (991.8 ±701.12 pg/mL). Mean (±SD) AUC\text{0—τ} values were also highest for the Duac–MP group (22177.5 ±17842.55 pg*hr/mL) and CLN 1%–BPO 3% group (17812.1 ±14733.01 pg*hr/mL), and lowest for the Duac–MPF group (13062.8 ±6714.40 pg*hr/mL). The differences in C\text{max} and AUC between CLN 1%–BPO 3% and the Duac–MP and Duac–MPF formulations were not statistically significant. However, the respective 90% confidence intervals for the ratio of geometric means of CLN 1%–BPO 3% versus Duac–MP and Duac–MPF were both outside the 80% to 125% bioequivalency range.

Systemic exposure to clindamycin sulfoxide was also measurable after application of all 3 formulations. The metabolite exposure for CLN 1%–BPO 3% was comparable to the Duac–MP formulation and was higher than the Duac–MPF formulation. Systemic exposure to clindamycin sulfoxide was lower relative to clindamycin, as mean C\text{max} and AUC values...
were approximately 4- to 5-fold higher on average for clindamycin compared with clindamycin sulfoxide. This ratio was comparable across all 3 formulations, indicating that the conversion of clindamycin to its metabolite is not affected by formulation.

The applicant has provided the following discussion on the above results:

The differences between the 3 formulations in C_{max} and AUC were likely related to the large intersubject variability in the clindamycin and clindamycin sulfoxide plasma concentrations observed in the study. The variability in percutaneous absorption of clindamycin was not unexpected based on differences in skin permeability and conditions between subjects with acne vulgaris; this variability has been well documented in other studies of topical clindamycin products (van Hoogdalem 1998; Akhavan and Bershad 2003). The systemic exposures to clindamycin were not statistically different (p>0.32) based on the prespecified ANOVA. It should also be noted that the intent of this study was to show the relative bioavailability of the 3 formulations and it was not powered to demonstrate bioequivalence of CLN 1%–BPO 3% to either Duac–MP, or Duac–MPF within the 80% to 125% range.

Maximum observed plasma concentrations of clindamycin in this study were highest in the Duac–MP group (≤5090 pg/mL; 5.09 ng/mL), followed by the CLN 1%–BPO 3% group (≤4140 pg/mL; 4.14 ng/mL) and Duac–MPF group (≤3560 pg/mL; 3.56 ng/mL). Overall, the systemic exposure to clindamycin observed in this study was very low and was well within the limits of exposure reported in other bioavailability studies with topical clindamycin in single-entity and combination formulations that are generally regarded as safe (van Hoogdalem 1998). In an earlier study that evaluated application of Duac–MP once daily (~1 gram/day) or clindamycin 1% solution twice daily (~0.7 gram/day) for 4 weeks, plasma levels of clindamycin during the application period were not significantly different (mean <0.5 ng/mL for both groups; mean in Duac–MP group ranged from 0 to 3.38 ng/mL) (Study S194-GB-01; data on file at Stiefel). Plasma concentrations of clindamycin after topical application of Clindagel were reported to be <5.5 ng/mL (Clindagel 2000), and after topical application of Cleocin T were reported to range from 0 to 3.0 ng/mL (Cleocin T 2005).

Results of this study were also comparable to maximum plasma concentrations of clindamycin after topical application of combination products containing clindamycin phosphate 1.2% and tretinoin 0.025%; Veltin gel ≤5.56 ng/mL, with 1 subject 8.73 ng/mL (Veltin 2010) and Ziana gel ≤3.5 ng/mL, with 1 subject 13.1 ng/mL (Ziana 2009). Additionally, the peak systemic exposure most commonly seen with topical clindamycin formulations (<10 ng/mL) is 250 times lower than the exposure observed after a single oral dose of clindamycin hydrochloride 150 mg capsule (2500 ng/mL) (Cleocin HCl 2007)

The mean C_{max} and AUC after administration of the CLN 1%–BPO 3% group was higher than that of Duac–MPF, the currently licensed product in Europe and lower than that of Duac-MP, currently licensed in US. However this study was not planned to demonstrate bioequivalence and the choice of subjects with acne introduced a large inter-subject variability and so no conclusions on the formulation effects on bioavailability can be made. The applicant was only planning to characterise the relative PK in the patient setting and did not plan to rely heavily on the clinical efficacy and safety data from the currently authorised Duac Gel. Hence the selected patient population for the relative PK study is acceptable.

From the applicant’s discussion it is reasonable to conclude that there is high variability in absorption of clindamycin after topical application as evidenced from published studies. The result of this study was broadly in line with the results of the published studies.
Based on the conclusion that systemic exposures were “broadly similar” between CLN 1%-BPO 3% (Duac LD gel) and Duac-MPF (Duac gel), the considerable safety data available from the European reference product (Duac gel) can be considered to be supportive for this application. Moreover the systemic exposure of clindamycin after topical administration is very low as compared to the systemic exposure after oral administration, which gives more reassurance for the acceptable safety of the proposed product.

**Pharmacodynamics**

No new studies/data have been submitted.

**Clinical Efficacy**

**Main Study – Study W0261-301**

This was a large, multicentre, randomised, double-blind, parallel-group, active- and vehicle-controlled study intended to evaluate the safety and efficacy of CLN 1%-BPO 3% relative to its individual active constituents (clindamycin 1% gel and BPO 3% gel) and to its vehicle (vehicle gel) in the treatment of acne when applied once daily for 12 weeks. The study consisted of 5 visits, including baseline (day 1), 3 interim visits (weeks 2, 4, and 8), and an end of study visit (week 12/early termination). Subjects were randomised (1:1:1:1:1) to each study product group.

Efficacy was evaluated through lesion counts (inflammatory, non-inflammatory, and total lesions), ISGA, and the subject’s global assessment (SGA). Efficacy assessments were performed at each study visit. When feasible, the same efficacy assessor was to perform all lesion count and ISGA assessments on the same subject at all visits to ensure consistency in the evaluations. Inflammatory lesions (ie, papules, pustules, and nodules) and non-inflammatory lesions (ie, open and closed comedones) were counted separately; the lesion counts were taken from the face (defined as the hairline edge to the mandibular line, including the nose). Total lesions were calculated as the sum of the inflammatory and non-inflammatory lesion counts.

This study included 2 co-primary efficacy endpoints:

- Absolute change from baseline to week 12 in lesion counts (inflammatory, non-inflammatory, and total).
- Proportion of subjects at week 12 who had a minimum 2-grade improvement from baseline in the ISGA score.

Secondary Endpoints:

- Percent change from baseline to week 12 in lesion counts (inflammatory, non-inflammatory, and total).
- Proportion of subjects with SGA scores of 0 or 1 at week 12.
- Proportion of subjects with ISGA scores of 0 or 1 at week 12.

Other Endpoints:

- Time to at least a 50% reduction in total lesion counts.
- Percent change in lesion counts (inflammatory, non-inflammatory, and total) from baseline to weeks 2, 4, and 8.
- Absolute change in lesion counts (inflammatory, non-inflammatory, and total) from baseline to weeks 2, 4, and 8.
- Proportion of subjects with ISGA scores of 0 or 1 at weeks 2, 4, and 8.
- Proportion of subjects with SGA scores of 0 or 1 at weeks 2, 4, and 8.

In order to demonstrate success, CLN 1%-BPO 3% must have been superior to clindamycin gel, BPO gel, and vehicle gel (2 sided, P <0.05 for each comparison) at week 12 in showing...
both a greater absolute change from baseline in 2 out of 3 lesion counts (inflammatory, non-inflammatory and total) and a greater proportion of subjects with a minimum 2-grade improvement from baseline in the ISGA score.

**Study Population**
A total of 1319 subjects were enrolled and assessed for eligibility across 24 investigational centres in the US, Canada, and Belize. Eligible subjects (N = 1315) included males and females who were 12 to 45 years of age. At baseline (day 1), subjects must have had facial acne with a minimum of 17 and not more than 60 total inflammatory lesions (papules and pustules, including nasal lesions), a minimum of 20 and not more than 150 non-inflammatory lesions (open and closed comedones, including nasal lesions), and an ISGA of 2 or greater.

**Results**
The co-primary and secondary lesion count (mean absolute and percent change from baseline to week 12 in inflammatory, non-inflammatory, and total lesions) and ISGA (2-grade improvement from baseline to week 12, and score of 0 or 1 at week 12) endpoints are presented in Table 3.

<table>
<thead>
<tr>
<th>Table 3: Co-Primary and Secondary Lesion Count and Investigator Static Global Assessment Endpoints (ITT)</th>
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<tbody>
<tr>
<td><strong>Inflammatory Lesions</strong>^a</td>
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<td>Mean absolute reduction</td>
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<td>Mean percentage reduction</td>
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<td><strong>Noninflammatory Lesions</strong>^a</td>
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<td>Mean absolute reduction</td>
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<tr>
<td><strong>Total Lesions</strong>^a</td>
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<tr>
<td>Mean absolute reduction</td>
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<tr>
<td>Mean percentage reduction</td>
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<tr>
<td><strong>Investigator’s Static Global Assessment, n (%)</strong></td>
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<tr>
<td>Minimum 2-grade improvement in ISGA from baseline to week 12</td>
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<tr>
<td>ISGA of 0 (clear skin) or 1 (almost clear skin) at week 12</td>
</tr>
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</table>

Source: Section 11.4.1 of the J0261-301 CSR (m5.3.5.1).
^a Lesion count change from baseline to week 12.
^b The last observation carried forward approach was used for missing week 12 evaluations.
^c Statistically significant difference compared with CLN 1%.BPO 3%.
^d Missing week 12 evaluations were considered failures.

**Co-Primary Endpoint Evaluation:**

- CLN 1%-BPO 3% was superior to clindamycin gel (P <0.001), BPO gel (P = 0.016), and vehicle gel (P <0.001) in regard to the proportion of subjects achieving a 2-grade improvement in ISGA from baseline to week 12 (ITT).

- The mean absolute reduction in inflammatory lesions observed in the CLN 1%-BPO 3% group was superior to the reductions observed in the clindamycin gel (P <0.001), BPO gel (P = 0.015), and vehicle gel (P <0.001) groups (ITT).
• The mean absolute reduction in non-inflammatory lesions observed in the CLN 1%-BPO 3% group was superior to the reductions observed in the clindamycin gel (P <0.001) and vehicle gel (P <0.001) groups, but not the BPO gel group (P = 0.102) (ITT).

• The mean absolute reduction in total lesions observed in the CLN 1%-BPO 3% group was superior to the reductions observed in the clindamycin gel (P <0.001), BPO gel (P = 0.032), and vehicle gel (P <0.001) groups (ITT).

Secondary Endpoint Evaluation:

• CLN 1%-BPO 3% was superior to clindamycin gel, BPO gel, and vehicle gel in the mean percent reductions in inflammatory lesions;
• CLN 1%-BPO 3% was superior to clindamycin gel and vehicle gel in the mean percent reduction of noninflammatory and total lesions (ITT and PP);
• CLN 1%-BPO 3% was also superior to clindamycin gel and vehicle gel in regard to the proportion of subjects with SGA scores of 0 or 1 at week 12
• CLN 1%-BPO 3% was superior to all 3 comparator products (clindamycin gel, BPO gel, and vehicle gel) in regard to the proportion of subjects with ISGA scores of 0 or 1 at week 12 (ITT and PP).

Other Endpoint Evaluation:

• The proportion of subjects who experienced at least a 50% reduction in total lesion counts was 75% in the CLN 1%-BPO 3% group followed by 70% in the BPO gel group, 59% in the clindamycin gel group, and 53% in the vehicle gel group (ITT).
• The Kaplan-Meier estimate of the time (in days) from baseline required to achieve at least a 50% reduction in lesion counts was calculated for the 50th percentile at 58, 82, 57, and 85 days in the CLN 1%-BPO 3%, clindamycin gel, BPO gel, and vehicle gel groups, respectively (ITT).
• At least a 50% reduction in lesion counts was achieved significantly earlier in the CLN 1%-BPO 3% group than in the clindamycin gel (P <0.001) or vehicle gel (P <0.001) groups (ITT).
• Overall, evaluation of the absolute and percent reductions in lesion counts, and the proportion of subjects with ISGA scores of 0 or 1 at weeks 2, 4, and 8 showed the increasing efficacy of CLN 1%-BPO 3% over time (ITT).

Supportive Efficacy Analyses:
Analyses including all randomised subjects and using each of the alternate methods of imputation for missing data continued to show that study W0261-301 met its co-primary endpoints.

Efficacy Conclusions
In regard to the ISGA, the results demonstrated that CLN 1%-BPO 3% is superior to clindamycin gel, BPO gel, and vehicle gel in the proportion of subjects who had at least a 2-grade improvement in ISGA. In regard to reductions in lesion counts, CLN 1%-BPO 3% was superior to clindamycin gel and vehicle gel in the reduction of all 3 lesion types, and was superior to BPO gel in the reduction of inflammatory and total lesions (ie, 2 of 3 lesion types). Therefore, the co-primary endpoints were met and the study demonstrated that CLN 1%-BPO 3% is effective for the treatment of acne when applied once daily for 12 weeks.
Given the statistically significant results in the primary, secondary and other evaluations conducted with the ITT analysis set, coupled with supporting results in the PP analysis set and in the post-hoc analyses, study W0261-301 demonstrated that CLN 1%-BPO 3% is effective in treating acne by reducing the number of inflammatory, non-inflammatory and total acne lesions, as well as by decreasing acne severity as determined by the investigator’s overall assessment. The results further demonstrated that both BPO and clindamycin contribute to the efficacy of the combination product and CLN 1%-BPO 3% is more effective in the treatment of acne than either of its individual active constituents alone.

The primary efficacy end-point was a co-primary end-point and has been met. Achieving a positive result on two primary endpoints rather than just one is a higher hurdle and no adjustment for multiplicity is required. The secondary end-points are largely supportive and in the direction of the primary end-point. The response of the efficacy endpoints in the 1% clindamycin arm and the 3% BPO arm (active controls) is higher than that in the vehicle group.

It is observed that Duac LD gel is not significantly better than 3% BPO alone in non-inflammatory lesions. This suggests that the BPO component is the only active component in the treatment of non-inflammatory acne. However as the pre-specified co-primary endpoints have been met, the study is considered conclusive on the efficacy of Duac LD gel.

This study therefore demonstrates that Duac LD gel is more efficacious in the treatment of acne ISGA grade ≥2 as compared to vehicle and the individual components 1% clindamycin and 3% BPO.

**Clinical Safety**

In support of safety for this product, the applicant provides the safety of Duac which was evaluated in 10 clinical studies. These included 4 phase 1 patch test studies (phototoxicity, photoallergy, cumulative irritation/contact sensitisation, and contact sensitisation [N=283 subjects]), a pharmacokinetic absorption/bioavailability study (N=77 subjects), and 5 safety and efficacy studies (N=1319 subjects). This has been assessed before during the assessment of Duac once daily gel (1% Clindamycin and 5% benzoyl peroxide).

An overview of the safety data from phase 3 study is provided here.

**Patient Exposure**

A total of 327 patients were exposed to the Duac LD gel in the phase 3 study, of which 186 patients had used the Duac LD gel for 12 weeks or more and more than 300 patients had used it for 8 weeks or more. This data combined with the considerably large body of safety data available for the higher strength Duac is considered adequate.

**Related Adverse Events**

The number of subjects who experienced study product-related AEs was low and was similar in each study product group: 4 subjects (1%) in the CLN 1%-BPO 3% group, 5 subjects (2%) in the clindamycin gel group, 8 subjects (2%) in the BPO gel group, and 5 subjects (2%) in the vehicle gel group. Most of the related adverse events are administration site reactions, which is along expected lines.

The apparent rationale for the development of this low dose Duac gel is to improve tolerability as compared to the currently available Duac gel. However this cannot be concluded as there is no direct comparative data between the two dose strengths.
Serious Adverse Events
There were no deaths in the study. One SAE (depression) was reported during the study. This event occurred in the BPO gel group, was of moderate intensity, and was considered unrelated to the use of the study product. Another SAE (possible stomach ulcer) was reported outside of the AE collection period;

Discontinuation due to adverse events
Five subjects discontinued study product use and were withdrawn from the study because of AEs. These events were primarily associated with application site reactions, including moderate dermatitis (CLN 1%-BPO 3%), moderate hypersensitivity (BPO gel), moderate pruritus (vehicle gel) and severe pruritus (BPO gel) that were considered related to study product use. The remaining subject (vehicle gel) experienced moderate varicella that was considered unrelated to study product use. Additionally, 10 subjects (2 each in the CLN 1%-BPO 3% and clindamycin gel groups and 3 each in the BPO gel and vehicle gel groups) experienced AEs that resulted in temporary interruptions of study product application.

The study discontinuation rates due to adverse events are too low to draw any conclusions, but the reported incidences between Duac LD gel and the vehicle are comparable. Again this data does not give rise to any safety concerns regarding Duac LD gel. The safety profile of Duac LD gel as emerging from the large phase 3 study is in line with the known safety profile of the currently available higher dose Duac gel. The phase 3 data does not present any safety concerns regarding the safety of Duac LD gel when used in the topical treatment of acne in 12-45 year age group for duration of up to 12 weeks.

Pharmacovigilance System
The RMS considers that the Pharmacovigilance System as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management Plan (RMP)
An updated Risk Management Plan which included the relevant details of the new dose strength has been submitted and is acceptable.

Clinical Expert Report
The clinical expert report is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Marketing Authorisation Application (MAA) Forms
The MAA form is medically satisfactory.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling
The SmPC, PIL and labelling are medically satisfactory and consistent with those for the currently marketed product.

Clinical Conclusion
There are no objections to the approval of this product from a clinical point of view.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Duac Once Daily 10 mg/g + 30 mg/g Gel are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical pharmacology studies were conducted which is acceptable. Non-clinical pharmacokinetics \((in\ vitro\ skin\ permeation)\) and toxicology \((in\ vivo\ ocular\ irritation)\) bridging studies have been conducted.

CLINICAL
The applicant has conducted a large, well planned, phase 3 study to compare the efficacy of Duac LD gel against vehicle and the individual components 1% clindamycin and 3% BPO. As no comparative efficacy data between the currently authorised Duac gel and the Duac LD gel is available, no conclusions on similar efficacy to currently authorised Duac gel can be made. The phase 3 study however conclusively shows that Duac LD is superior to vehicle and the individual components on the pre-specified co-primary endpoints and as stated before the efficacy of individual components have been accepted before as seen in the number of products currently authorised. It is noted that that both the 1% clindamycin and 3% BPO treatment arms also have a higher response as compared to vehicle.

There are some formulation changes between the two strengths of Duac gel which might affect the systemic exposure of clindamycin, the applicant has conducted a relative bioavailability study. This study is largely inconclusive, however the results suggest that the systemic exposures of clindamycin after topical administration of both the strengths may be similar within a broad range due to high intersubject variability after topical absorption to acne lesions of varying severity. This observation is further supported by other published studies which report similar ranges of systemic exposure of clindamycin after topical administration. Therefore the available safety data of the higher dose strength is supportive of the safety of the lower dose strength. In addition, a reasonable level of safety data from the phase 3 study is available for Duac LD gel which confirms that it has acceptable safety. Duac –LD gel has a beneficial treatment effect on acne lesions with acceptable safety and therefore the benefit-risk is considered to be favourable.

PRODUCT LITERATURE
The SmPC, PIL and labelling are satisfactory and consistent with those for the reference product, where appropriate, and consistent with current guidelines.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with clindamycin phosphate and hydrous benzoyl peroxide is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<th>Application type</th>
<th>Scope</th>
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