Decentralised Procedure

RMS Day 210 Final Assessment Report

OVERVIEW

Bezak 10mg/50 mg v 1 g gel
Klindamicin/benzoilperoksid Jadran 10mg/50 mg v 1 g gel
Klindamicin/benzoilperoksid JGL 10mg/50 mg v 1 g gel

Clindamycin & Benzoyl Peroxide

SI/H/0217/001/DC
SI/H/0218/001/DC
SI/H/0219/001/DC

Applicant: Jadran - Galenski laboratorij d.d.

Reference Member State	Slovenia (SI)
Re-Start of the procedure:	March 12th, 2021
Date of this report:	June 24th, 2021

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ADMINISTRATIVE INFORMATION

Proposed name of the medicinal product(s) in the RMS	Bezak 10 mg/50 mg v 1 g gel Klindamicin/benzoilperoksid Jadran 10 mg/50 mg v 1 g gel Klindamicin/benzoilperoksid JGL 10 mg/50 mg v 1 g gel
Name of the drug substance (INN name):	Clindamycin Phosphate & Benzoyl Peroxide, Hydrous
Pharmaco-therapeutic group (ATC Code):	Antiinfectives for treatment of acne; D10AF51
Pharmaceutical form(s) and strength(s):	Gel; 10 mg/g & 50 mg/g
Reference Number(s) for the Decentralised Procedure	SI/H/0217/001/DC SI/H/0218/001/DC SI/H/0219/001/DC
Reference Member State:	Slovenia (SI)
Member States concerned:	SI/H/0217/001/DC: HR & IE SI/H/0218/001/DC: AT & DE SI/H/0219/001/DC: ES; IT & PT
Legal basis of application:	10(3)
Applicant (name and address)	Jadran - Galenski laboratorij d.d. Svilno 20 Rijeka; 51000 Croatia
Names and addresses of all manufacturer(s) responsible for batch release in the EEA	JADRAN - Galenski laboratorij d.d. Svilno 20 51000 Rijeka Croatia
Names and addresses of all manufacturer(s) of the medicinal products	JADRAN - Galenski laboratorij d.d. Svilno 20 51000 Rijeka Croatia
Names and addresses of all manufacturers of the active substance	[redacted]

	[redacted]
Names and addresses of all ASMF holders (if different from manufacturer of active substance)	*N/A*
Names and addresses of all CEP holders (if different from manufacturer of active substance)	[redacted]
Names and addresses of contract companies used for clinical trials (CRO(s))	*N/A*
RMS contact person:	**Name** [redacted] Tel: Email:
Names of the assessors:	**Quality**: **Name(s)** [redacted] Tel: Email: **Non-clinical**: **Name(s)** [redacted] Tel: Email: **Clinical**: **Name(s)** [redacted] Tel: Email: **Pharmacovigilance/Risk Management Plan:** **Name(s)** [redacted] Tel: Email:

	Product Information: **Name(s)** [redacted] Tel: Email: **Readability:** **Name(s)** [redacted] Tel: Email:

I. RECOMMENDATION

Based on the review of the data and the Applicant's response to the questions raised by RMS and CMSs on quality, safety and efficacy, the RMS considers that the applications for Clindamycin/Benzoyl Peroxide 10 mg/g + 50 mg/g gel indicated for the topical treatment of mild to moderate acne vulgaris, particularly inflammatory lesions, in adults and adolescents aged 12 years and above,

are approvable.

II. EXECUTIVE SUMMARY

II.1 Problem statement

Not Applicable. This is a 10(3) application.

II.2 About the product

ATC Code: D10AF51
Pharmacotherapeutic group: Antiinfectives for treatment of acne

Mode of action:
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.

Claimed indication is:
Clindamycin/Benzoyl Peroxide 10 mg/g + 50 mg/g gel is indicated for 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.

For detailed description of the posology, adverse effects, contraindications etc., please refer to the SmPC.

II.3 General comments on the submitted dossier

This decentralised Procedure Application concerns gel containing 10 mg/g of Clindamycin & 50 mg/g of Benzoyl Peroxide. The active substances are not considered as new active substances. The Applications are submitted according to Article 10(3) (hybrid application) Directive 2001/83/EC (as amended). The reference medicinal product (brand leader) referred to as authorised not less than 10 years in EEA is DUAC Akne Gel, authorised in Germany since December 13th, 2004, by GlaxoSmithKline GmbH & Co. KG 80700 München (MA No.: 60964.00.00).

In this Assessment Report, the common name Clindamycin/Benzoyl Peroxide 10 mg/g + 50 mg/g gel is used. However, this report also applies to the initial and duplicate applications for Clindamycin/Benzoyl Peroxide containing products.

With Slovenia as the Reference Member State in these Decentralised Procedures, the applicant Jadran - Galenski laboratorij d.d. is applying for the Marketing Authorisations for Clindamycin and Benzoyl Peroxide containing gel in the following CMSs:

SI/H/0217/001/DC: HR & IE
SI/H/0218/001/DC: AT & DE
SI/H/0219/001/DC: ES; IT & PT

The applicant has followed current CHMP guidance documents. Essential similarity with DUAC Akne Gel (clindamycin and benzoyl peroxide)(GlaxoSmithKline GmbH, Germany) is claimed based on 4 pivotal *in vitro* studies and 1 supportive therapeutic equivalence trial.

Scientific Advice was given by SI and UK authorities. Recommendations in the Scientific Advice Letters were NOT taken into account by the Applicant.

Applicant is referring to the European Reference Product (ERP) in RMS (SI) and CMS AT. Reference is made to the reference product DUAC Akne Gel, authorised in Germany (MA No.: 60964.00.00). The ERP information was circulated during validation period.

According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

No formal Environmental Risk Assessment has been provided. Since Clindamycin/Benzoyl Peroxide 10 mg/g + 50 mg/g gel will be used as a substitute for the reference medicinal product, its introduction to the market will most likely not lead to an increased exposure to the environment.

II.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles.

The RMS has been assured that acceptable standards of 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.

For the manufacturer of finished product, primary and final packaging, testing and batch release site: JADRAN - Galenski laboratorij d.d., Rijeka, Croatia, references were given to the EudraGMDP for Marketing Authorisation and GMP Certificate issued by Croatian Authority.

Regarding the statement on GMP for the active substances declarations are provided from the manufacturer responsible for manufacture of the finished product and batch release situated in the EU.

[redacted]

GCP
A statement of GCP compliance has been enclosed for the supportive therapeutic equivalence study (No ZERKALIN-04/2018). The Applicant has been asked to provide the outcomes of GCP inspection of the study sites.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

These applications concern gel containing 10 mg/g + 50 mg/g of Clindamycin and Benzoyl Peroxide respectively. Based on assessment of the documentation and Applicant's responses, marketing authorisations can be granted.

III.1 Quality aspects

[redacted]

III.2 Non-clinical aspects

Pharmacology/Pharmacokinetics/Toxicology
There are no objections to the approval of Clindamycin/Benzoyl Peroxide 10 mg/g + 50 mg/g gel from the non-clinical point of view. Pharmacodynamic, pharmacokinetic and toxicological properties of clindamycin and benzoyl peroxide are well known. As clindamycin and benzoyl peroxide are a widely used, well-known active substances, the applicant has not provided additional studies and further studies are not required. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.
The non-clinical aspects of the SmPC are in line with the SmPC of the reference product.

Environmental Risk Assessment (ERA)
Since Clindamycin/Benzoyl Peroxide 10 mg/g + 50 mg/g gel will be used as a substitute for the reference medicinal product, it will most likely not lead to an increased exposure to the environment. The consumption data for DUAC in the last four years demonstrated no increase in consumption in Croatia. The presented data therefore confirm that the absence of a formal environmental risk assessment for Clindamycin/Benzoyl Peroxide 10 mg/g + 50 mg/g gel is justified.

III.3 Clinical aspects

Clindamycin 1% + benzoyl peroxide (BPO) 5% gel JGL (clindamycin as clindamycin phosphate 10 mg/g + anhydrous benzoyl peroxide 50 mg/g) is intended for topical treatment of acne vulgaris (mild-to-moderate papulopustular acne in adults and adolescents 12 years of age and older).
Clindamycin 1% + benzoyl peroxide (BPO) 5% gel JGL was developed after the reference product by GlaxoSmithKline (Duac/ Clindoxyl/Indoxyl 1%/5% gel). It is pharmaceutically equivalent to the reference product in the sense of the identical qualitative and quantitative composition of the active and inactive ingredients, [redacted].
In the process of demonstration of therapeutic equivalence of the product Clindamycin 1% + benzoyl peroxide (BPO) 5% gel JGL vs. the reference product, the applicant (JGL) has generated pivotal and supportive data:

Pivotal
(i) Comparative (T vs. R) in vitro release studies to document extended pharmaceutical equivalence;

(ii) Comparative (T vs. R) in vitro penetration and permeation studies in human skin samples;

(iii) Comparative (T vs. R) in vitro pharmacodynamics study – antibacterial activity in the human skin disk antibiogram model.

Supportive

(i) A randomized, open-label, 12-week comparative trial (T vs. R) in adults and adolescents with mild-to-moderate papulopustular (inflamed) acne.

The SmPC is in accordance with the innovator's SmPC and is acceptable.
The clinical overview on the clinical pharmacology, efficacy and safety has been adequately updated.

***In vitro* studies to support therapeutic equivalence**

The following in vitro studies have been performed to support extended pharmaceutical equivalence and equivalence with respect to efficacy:

- Comparative evaluation of *in vitro* release of Clindamycin and 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

In vitro release tests compared the *in vitro* release rate of clindamycin and benzoyl peroxide from test and reference products across a synthetic membrane. The results of *in vitro* release studies with synthetic membrane on Enhancer cells as well as *in vitro* release data obtained on Franz cells confirm that the release rate of both clindamycin and benzoyl peroxide from test product are comparable with the reference product. The Applicant addressed several issues raised during the initial assessment. The missing study reports for *in vitro* release testing have now been enclosed. Certain critical information regarding method and validation performance were provided. Additionally, questions were also adequately addressed regarding the method validation procedure, experimental conditions, as well as statistical analysis and data interpretation.

A comparative evaluation of *in vitro* antibacterial activity of clindamycin with benzoyl peroxide in test and reference formulation was performed to demonstrate pharmacodynamic equivalence. A skin diffusion antibiogram method was developed to simulate *in vivo* conditions. The test was performed using basal agar inoculated with *Propionibacterium acnes*. Sterilized dermatomized skin discs with reference or test product were placed on the inoculated agar plates and the survival of the pathogen growing on the basal agar plates in the presence of the skin discs was evaluated measuring the diameter of the inhibition zones. The bacteriostatic/bactericidal activity was compared between the formulations by measuring the zone of inhibition. The inhibition zone was proportional to the amount of antibiotic absorbed through the skin (and released in the agar) and to the antibacterial activity of the antibiotic. The 90% confidence interval for the ratio of measured values for reference and test product was within the limits of 0.8 to 1.25. On this basis, equivalence between test and reference product regarding antibacterial activity was concluded. Certain issues were raised and addressed by the Applicant regarding method validation, study procedure and data analysis.

In vitro skin permeation study was performed to demonstrate the equivalence of permeation kinetics of both benzoyl peroxide and clindamycin between test and reference products. The study was performed on human excised skin, mounted onto a Franz cell, to simulate the permeation and penetration processes of active ingredients into and across human skin under *in vivo* conditions. Permeation through the human skin tissue into the acceptor medium was monitored over a period of 48 hours. No significant permeation though human skin into acceptor medium was reported for either active ingredient or metabolism product benzoic acid for both test and reference products. Deficiencies regarding method validation, as well as study procedure, were now addressed by the Applicant.

The Applicant provided an overview of the development, procedure and results of *in vitro* skin penetration testing of the proposed product in comparison with the reference product. The Applicant concluded that there was no statistical difference for the skin penetration (from 12 different donors) of clindamycin, benzoyl peroxide and benzoic acid, between test and reference formulations.

Furthermore, minimal fraction of the amount of test and reference product applied during testing was found in both epidermal and dermal layer.
It is important to note that significant deficiencies were observed regarding method development and optimisation, study design and method validation. Due to inappropriate method development, stratum corneum could not be quantified separately from epidermis. That being said, stratum corneum sampling is not recommended as an appropriate method for pharmacokinetic evaluation of drug products that target primarily the cutaneous appendages (e.g. hair follicles, sebaceous glands), which is the case for the proposed product. Additionally, negligible systemic absorption detected during maximum absorption testing, and minimal rate of penetration of the reference product is described in literature. Since the proposed and reference product are qualitatively and quantitatively the same ([redacted]), additional *in vivo* penetration testing was deemed unnecessary.

Supportive data (randomized, open-label, 12-week comparative trial in adults and adolescents with mild-to-moderate papulopustular (inflamed) acne)

Additionally, as supportive data, the Applicant reported an open-label, phase III, randomized, parallel-group comparative study, assessing the efficacy and safety of Zerkalin® Intensive, gel for cutaneous use (manufacturer: JADRAN GALENSKI a. o., Croatia), and Indoxyl®, gel for cutaneous use (manufacturer: Glaxo Operations UK Ltd., UK), in acne patients. The clinical study has been conducted for previous specific regulatory purposes and can only serve as supportive evidence, since it was not conceived as a formal therapeutic equivalence trial (no predefinition of margin of equivalence, no sample size determination). The trial was also open-label and it did not include a placebo arm to guarantee assay sensitivity. Nevertheless, some evidence is present and points to comparable efficacy and safety profiles of the test and reference products. Several issues regarding the trial were adequately addressed.

Several questions have been raised by the CMS clinical assessors. which have all been addressed by the Applicant. The Applicant's responses to these issues are deemed adequate by the RMS.

There are no outstanding issues regarding the clinical aspects of the proposed medicinal product.

Summary Pharmacovigilance system

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

Risk Management Plan

The MAA has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Clindamycin/Benzoyl Peroxide 10 mg/g + 50 mg/g gel.

Safety specification

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

There are no risks considered important for inclusion in the list of safety concerns in the RMP. The summary of safety concerns is in line with that of the reference product and is considered acceptable.

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the Applicant, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP

The submitted Risk Management Plan, version 0.2, signed 27.3.2021 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

Periodic Safety Update Report (PSUR)

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.

- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.

- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

Common renewal date
Applicant proposed CRD to be 5 years after the end of registration procedure. This is acceptable for RMS, if the Applicant is referring to the end of international phase of the Decentralised procedure.

IV. BENEFIT RISK ASSESSMENT

These applications concern gel containing 10 mg/g + 50 mg/g of Clindamycin and Benzoyl Peroxide

respectively. The **overall risk/benefit ratio** for these Applications is considered **positive.** Therefore, marketing authorisations can be granted.

V. PROPOSED LIST OF OUTSTANDING ISSUES

V.1 Quality aspects

V.2 Non-clinical aspects

Major objections
Pharmacology
None.

Pharmacokinetics
None.

Toxicology
None.

Other concerns
Pharmacology
None.

Pharmacokinetics
None.

Toxicology
None.

V.3 Clinical aspects

Major objections
None.

Other concerns
None.

VI. PROPOSED CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

VI.1 Legal Status

- Subject to medical prescription

VI.2 (Draft) final list of recommendations not falling under Article 21a/22 of Directive 2001/83 in case of a positive benefit risk assessment

N/A

VI.3 Proposed list of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

- **Additional risk minimisation measures (including educational material)**

  N/A

- **Obligation to conduct post-authorisation measures in accordance with Article 21a of Directive 2001/83**

  N/A

- **Specific obligation to complete post-authorisation measures for the marketing authorisation under exceptional circumstances in accordance with Article 22 of Directive 2001/83/EC**

  N/A

VI.4 Module I – Application related comments (including product name)

Product name

RMS' day 70 comment
SI/H/0217/001/DC
Aknet Duo 10 mg/g + 50 mg/g gel is not acceptable as it is to similar to the names of authorised products Belakne and Akineton. Moreover, qualifier "Duo" is not justified as there mono-component MP is not authorised. According to JAZMP guideline on product names;
https://www.jazmp.si/fileadmin/datoteke/dokumenti/SRZH/Poimenovanje_zdravil20111028.pdf
the name of MP should be consisted of single word only. Additionally, the expression of strength should be corrected in accordance JAZMP guideline:
https://www.jazmp.si/fileadmin/datoteke/dokumenti/SRZH/Izrazanje_jakosti.pdf

SI/H/0218/001/DC
TopiDual 10 mg/g + 50 mg/g gel is not acceptable as in writing and in pronunciation resembles to closely to the name of already authorised MP Tapidola. Difference is only in 2 letters. Kapital letter should not be used within the names of MPs. Additionally, the expression of strength should be corrected in accordance JAZMP guideline:
https://www.jazmp.si/fileadmin/datoteke/dokumenti/SRZH/Izrazanje_jakosti.pdf

SI/H/0219/001/DC

Klindamicin/benzoilperoksid JGL 10mg/50 mg v 1 g gel Applicant should present official proof of the acceptance of shortened name of the Applicant or trade mark.

Applicant's d106 response
Applicant proposed new names and revised Annexes 5.19.

RMS' day 120 comment
Newly proposed names Bezak (SI/H/0217/001/DC), Klindamicin/benzoilperoksid Jadran (SI/H/0218/001/DC) and Klindamicin/benzoilperoksid JGL (SI/H/0219/001/DC) are acceptable for RMS. Issue resolved.

VI.5 Summary of Product Characteristics (SmPC)

SmPC is now acceptable.

VI.6 Package Leaflet (PL)

VI.6.1 Package Leaflet

PL is acceptable.

VI.6.2 Assessment of User Testing

In the day 70 RMS' Preliminary Assessment Report (PrAR) The Assessment of User Testing submitted by the applicant was considered acceptable.

VI.7 Labelling

The labelling texts are acceptable.