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Public Assessment Report

Scientific discussion

CLOBETASOL BELUPO
(clobetasol propionate)

SK/H/0308/001/DC

Date: October 2025

This module reflects the scientific discussion for the approval of CLOBETASOL BELUPO. The procedure was finalised on 23 August 2024 (D210). For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for **CLOBETASOL BELUPO, shampoo, 500 micrograms/g** from the applicant Belupo lijekovi i kozmetika, d.d..

The medicinal product is indicated for topical treatment of moderate scalp psoriasis in adults.

A comprehensive description of the indication and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

The product is viscous, semi-transparent, colourless to pale yellow liquid shampoo with an alcoholic odour. It is packed in white bottle made out of HDPE (filling volume is 60 ml or 125 ml) with tamper-proof PP closures with top-opening.

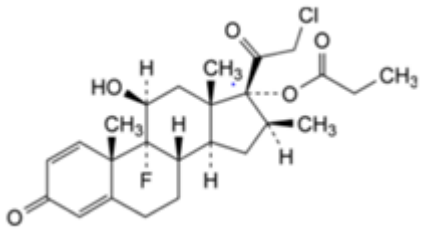
The active substance is clobetasol propionate and the other ingredients are:

Ethanol 96 %
Sodium laureth sulfate
Coco alkyl dimethyl betaine
Polyquaternium 10
Citric acid monohydrate
Sodium citrate
Purified water

II.2 Drug Substance

INN: Clobetasol propionate

Active substance structure:



Chemical name: 21-Chloro-9-fluoro-11β-hydroxy-16β-methyl-3,20-dioxopregna-1,4-dien17-yl propanoate

Appearance: white to almost white, crystalline powder

Solubility: practically insoluble in water, freely soluble in acetone, sparingly soluble in ethanol (96 %)

Manufacturing: the active substance clobetasol propionate is a well-known substance described in the Ph.Eur. Monograph No.2127. Both drug substance manufacturers are holders of Ph. Eur. Certificates of Suitability.

Specifications: sufficient compiled specification from drug product manufacturer was provided. Batch analyses from both manufactures were in compliance with the specification.

Stability: the re-test period of the substance form is 60 months if stored in double PE bags in Al foil bag, with silica gel bags in between, placed in a PE drum or in double PE bags placed in a fibre, plastic or aluminium container.

II.3 Medicinal Product

Pharmaceutical development

The product was developed on the basis of the reference product sourced in the EU.
Bioequivalence study was not performed. Demonstration of equivalence with respect to quality was conducted according to Draft guideline on quality and equivalence of topical products (CHMP/QWP/708282/2018). Quality equivalence parameters include pharmaceutical form, method of administration, qualitative and quantitative composition and physicochemical/ rheological properties.

Manufacturing

Aim of manufacturing process development was the selection of optimal process parameters to obtain reproducible manufacturing process and product quality. The care was taken to define the optimal order and conditions for addition of surfactants. Appearance and foam generation were main parameters for evaluation step for adding of surfactants. The manufacturing process phases were sufficiently discussed.

Product specification

In-process control specification includes critical parameters that are monitored during whole manufacturing process.
The proposed parameters of specification are suitable to control the quality of the product. Selection of physical parameters, such as pH, density, viscosity are suitable for testing of the drug product according to Draft guideline on quality and equivalence of topical products (CHMP/QWP/708282/2018) and Ph. Eur (0132). Parameter for microbial purity is in compliance with Ph.Eur. 5.1.4 (preparation for cutaneous use).
Analytical methods used for drug product were adequately described. Validation of in-house analytical methods used for drug product control has been provided.
Limits for related substances and viscosity have been set according to the batch and stability data.

Stability

Based on 12-month stability data in long-term, intermediate and accelerated conditions, a shelf life of 24 months was accepted. Drug product does not require any special temperature storage conditions. Results from photostability study showed drug product is sensitive to light so it should be stored in the original package to protect from light. In-use stability data provided support 6-month in-use shelf-life of the drug product.

II.4 Discussion on chemical, pharmaceutical and biological aspects

From a quality point of view the dossier was generally well presented and processes appeared to be well controlled.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of clobetasol propionate are well known. As clobetasol propionate is a widely used, well-known active substance, the applicant has not provided additional studies, and further studies were not required. An overview based on the literature review was, thus, appropriate.
The instructions on use of the drug product during pregnancy and lactation, the effect on fertility from a non-clinical perspective, and the preclinical safety data contained in the SmPC reflect the characteristics of the API and are in line with the reference product´s SmPC. The applicant summarized the safety aspects of sodium laureth sulfate and reflected its content and relevant skin and eye effects on safety in section 4.4 of the SmPC.
The Non-Clinical Overview on the pre-clinical pharmacology, pharmacokinetics and toxicology was adequate.

III.2 Ecotoxicity/environmental risk assessment (ERA)

It is acknowledged that the active substance is a corticosteroid that belongs to the endocrine active substance, and tailored ERA, irrespective of predicted environmental concentration, should be applied.

Although, considering the hybrid application and number of other topical products already placed on the market in some of concerned member states, and PECsw values below the action limit and 3R principles, no further ERA studies were required.

III.3 Discussion on the non-clinical aspects

From a non-clinical point of view the provided data were considered adequate.

IV. CLINICAL ASPECTS

IV.1 Introduction

The clinical overview contained justification for biowaiver and bibliographic review for clobetasol propionate in different pharmaceuticals forms including shampoo in respect to the efficacy and safety profile. No new study of therapeutic equivalence, nor bioequivalence study have been conducted.

IV.2 Pharmacokinetics

Biowaiver
The comparative test between test and reference product to evaluate physicochemical and rheological properties as pH, relative density, viscosity, foam analysis, texture analysis and evaporation test was provided and confirmed comparable results between proposed product and the reference product.

Based on equivalent qualitative composition, quantitative composition and comparable physical and rheological properties to the reference product, the applicant applied for waiver of the need to provide efficacy equivalence data, permeation kinetic or pharmacodynamic studies, safety and local tolerance studies.
In addition, equivalence with respect to efficacy and safety was discussed.

Equivalence with respect to efficacy
CLOBETASOL BELUPO 500 micrograms/g shampoo meets criteria for biowaiver - exemption from method which demonstrate the efficacy equivalence (permeation kinetics studies and pharmacodynamic

studies) as follows:
- The product is a liquid shampoo pertaining to simple formulations with a single-phase base in which the active substance is in solution.
- The product is intended for cutaneous use on the scalp only with a purpose that the active substance is administered on the skin surface.
- CLOBETASOL BELUPO 500 micrograms/g shampoo has the same qualitative and quantitative composition of excipients as the reference product.

Equivalence with respect to safety
CLOBETASOL BELUPO 500 micrograms/g shampoo contains the active substance with well-known properties. Excipients used in this formulation are well-established and the same ones as in the reference product.
The reference product information reveals acceptable safety profile considering that systemic and local adverse reactions mostly occur with uncommon frequency (in less than 1 of 100 patients) and rated as mild to moderate.

Conclusion of justification for biowaiver
Since the proposed product is liquid shampoo pertaining to simple formulations with a single-phase base in which the active substance is in solution, with the same qualitative and quantitative composition of active substance and excipients and the demonstration of equivalence with respect to quality has been provided, there was no need to provide equivalence data in respect of efficacy, safety or pharmacodynamic studies. Thus, the biowaiver for providing such data was accepted.

IV.3 Risk Management Plan

The MAH 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 CLOBETASOL BELUPO.

- Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

Pharmacovigilance Plan
The applicant has proposed routine pharmacovigilance. No additional pharmacovigilance activities have been proposed. The routine pharmacovigilance was accepted.

Risk minimisation measures
The safety information in the approved product information is aligned to the reference medicinal product. No additional risk minimisation activities have been proposed by the applicant, which was endorsed.

IV.4 Discussion on the clinical aspects

Submitted clinical dossier was of sufficient quality. Submitted data supported the chosen legal basis “hybrid application”.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.
The results showed that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The test consisted of a pilot test with 4 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

This was the application for a marketing authorisation of medicinal products for human use as it is defined in Article 10(3) (hybrid application) of the European Directive 2001/83/EC as amended. Decentralised procedure according to Article 28(3) of Directive 2001/83/EC as amended with Slovak Republic acting as RMS. With the Slovakia as the Reference Member State the applicant Belupo lijekovi i kozmetika, d.d. was applying for the marketing authorisation in the following CMS: CZ, HR, PL, SI. The applicant has submitted the MAA under procedural number SK/H/0308/001/DC.

A European Reference Product was used in CMS HR and SI: Clobex 500 mikrogramov/g šampón, MAH: Galderma International, France, registered in SK on 22nd January 2007.
The justification to use this product was based on RMS's own files.

The applicant applied for biowaiver of providing bioequivalence study and additional kinetic/pharmacodynamic studies, safety and local tolerance studies based on similar qualitative and quantitative composition and based on similarity of physicochemical and rheological properties. The justification of the applicant was sufficient.

Scientific Advice was given to the applicant by HALMED Croatia. The scope of the questions and the rational for the advice was focused on planned biowaiver and legal basis. There was no discussion in the CMDh.

Agreement between the member states was reached during a written procedure. Based on submitted data the member states have considered the application as approvable and have therefore granted marketing authorisation. The decentralised procedure was finalised with positive outcome on 23 August 2024.