CBG MEB

Public Assessment Report

Scientific discussion

Eczoria 0.5 mg/g cream

(clobetasol propionate)

NL/H/3526/001/DC

Date: 16 March 2017

This module reflects the scientific discussion for the approval of Eczoria 0.5 mg/g cream. The procedure was finalised on 27 October 2016. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

A list of literature references is given on page 10-11.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Eczoria 0.5 mg/g cream from Exeltis Healthcare S.L.

The product is indicated for:

- Psoriasis (excluding plaque psoriasis).
- Recalcitrant eczema.
- Lichen planus.
- Discoid lupus erythematosus and other skin conditions that do not respond satisfactorily to less active steroids.

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

Clobetasol propionate is a highly active corticosteroid with anti-inflammatory, anti-pruritic, and vasoconstricting activity. The most significant effect of clobetasol propionate on skin is a non-specific anti-inflammatory response, partially due to vasoconstriction and decreased collagen synthesis. Topically applied clobetasol propionate can be absorbed through normal intact skin.
Percutaneous penetration of clobetasol propionate varies among individuals and can be altered by using different vehicles. It can be increased by use of occlusive dressings and by presence of inflammation and/or other disease of the epidermal barrier.

Clobetasol propionate 0.5 mg/g cream was developed initially by GlaxoSmithKline and registered in Spain under the trade name Clovate by UCB Pharma, S.A, in December 1981. In addition, there are different cobetasol propionate creams approved in other countries. There are also other formulations such as ointment, lotion, spray, shampoo, scalp application and foam of clobetasol propionate available.

This decentralised procedure concerns a bibliographic application based on the well-established medicinal use clobetasol. No new (pre)clinical studies were conducted. The MAH submitted non-clinical and clinical overviews based on scientific literature.

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

The concerned member states (CMS) involved in this procedure were Czech Republic, Finland, Hungary, Poland and Slovakia.

II. QUALITY ASPECTS

II.1 Introduction

Eczoria 0.5 mg/g is a soft white cream (as oil/water emulsion), with pH 4.7-5.7. Each gram of cream contains 0.5 mg of clobetasol propionate (which is equivalent to 0.44 mg clobetasol).

The cream is packed in 15 g and 30 g collapsible aluminium tubes, internally coated with an epoxy resin-based lacquer and sealed with a HDPE screw cap. The tube is equipped with membrane and the screw cap with piercer.

The excipients are: propylene glycol, glycerol monostearate 40-55, cetostearyl alcohol, glycerol monostearate 40-55 and polyethylene glycol stearate 100 (Arlacel 165), bees wax white, chlorocresol, sodium citrate dihydrate, citric acid monohydrate, purified water.

II.2 Drug Substance

The active substance is clobetasol propionate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white to almost white crystalline powder, practically insoluble in water, freely soluble in acetone and sparingly soluble in ethanol (96%).

The active substance does not exhibit polymorphism.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The specification of the MAH is according to the Ph. Eur. monograph and the additional residual solvent test and limits on the CEP. The specification limits have been adequately justified, including the limits for particle size distribution, which are according to the batch results of at least the results of the test & reference batches in the equivalence studies. Sufficient batch analysis results have been provided.

Stability of drug substance
Stability data have been provided on three production batches. The batches were stored during 6 months at 40ºC/75% RH and 48 months at 25 ºC/60%RH, according to ICH study design, packaged in the approved container closure system. Based on the stability results, a five years re-test period with no special temperature storage conditions is considered approvable.

II.3 Medicinal Product

Pharmaceutical development
The choice of excipients is justified and their functions explained. It has been adequately demonstrated that the quality of the products in the pivotal 'well established use' literature (including the originator/reference product Clovate) can be transferred to the proposed product. The quantitative compositions are similar, and it has been demonstrated that chemical-physical quality aspects critical for low dosed creams with the drug substance suspended, which in part may impact penetration (rate) into the skin (e.g. pH, viscosity, particle size drug substance, emulsion droplet size) are also comparable. Based on similarity of quality, bridging to the literature of clobetasol is sufficiently justified.

Manufacturing process
The manufacturing process has been described, including the experimental conditions and some in-process controls. The process consists of producing of an oil/water emulsion from a water phase and oily phase while stirring at elevated temperatures. The in-process controls included are adequate; they also include physicochemical parameters critical for preparation of low dosed creams with suspended drug substance. Adequate process validation studies are submitted of six production scale batches, with results on the relevant critical quality aspects during the process runs.

Control of excipients
The excipients comply with the Ph.Eur. These specifications are acceptable.

Microbiological Attributes
Microbiological monitoring is conducted as part of the release tests carried out on each batch of finished product. To avoid and prevent product contamination, chlorocresol has been selected as a preservative ingredient. Results have been provided of the Ph. Eur. preservative efficacy test performed according to Ph. Eur., with the product stored during the proposed shelf-life.

Quality control of drug product
The product specification includes tests for appearance, identity, assay, content preservative, pH, density, viscosity, spreadability, droplet size, degradation products, microbiological control and tightness of container closure. The release and shelf-life requirements/limits are identical except regarding some of the degradation products of which the shelf-life limits are wider. The analytical methods have been adequately described and validated.

Batch analytical data are provided on eight production batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product have been provided for six production-scale batches. The batches have been stored up to 24 months at 25°C/60%RH and 30°C/65%RH, and for 6 months at 40°C/75%RH.
The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed package. All parameters were well within the proposed specification limits. Assay decreased according to the included stability overage, and increase of degradation products was in mass balance with the assay. A photostability study has been performed, according to ICH Q1B guideline; the product is not susceptible to light when it is contained in the packaging.
Based on the stability results, a shelf-life of 24 months is justified. The storage conditions are 'store below 30°C, do not freeze', in the approved tube (aluminium tube with HDPE cap).
The claimed in-use storage period (two months) has been sufficiently justified based on the results of in-use stability testing. The batches used had been stored up to near the end of the shelf before initiation of the in-use study.

Specific measures for the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Eczoria 0.5 mg/g cream has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.
No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology, pharmacokinetics and toxicology

This application concerns a bibliographical application based on well-established medicinal use of clobetasol propionate. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Eczoria is intended for substitution of similar products on the market. The MAH has indicated that there is no significant concern to freshwater from the use of the new formulation and its addition to environmental exposure is considered to be minimal in relation to pre-existing uses. Therefore, there will be a negligible increase in the active substance released into the environment over and above existing quantities, no increase in environmental burden is anticipated and the calculated risk characterisation ratio is within the acceptable limits. Therefore no environmental risk assessment is deemed necessary.

IV. CLINICAL ASPECTS

IV.1 Introduction

Clobetasol propionate is a well-known active substance with established efficacy and tolerability. Creams and other topical formulations have been registered for decades.

For this bibliographic application a clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data.

IV.2 Pharmacokinetics

The MAH has presented literature data with respect to the penetration of clobetasol after application of different formulations with clobetasol. The main issue discussed is the large difference in amount of drug penetrated in the skin after application of different forms like cream, foam, lotion or cutaneous solution. For example, also based on *in vitro* studies, it has been described that clobetasol propionate formulated in foam reaches higher concentrations and higher permeation rate than the cream, cutaneous solution or lotion formulations. Also the penetration can be altered by the use of occlusive dressings, the thickness of each individual's skin, a case of inflammation or a particular skin condition.

Beside the influence of the formulation the decision of the agent depends on patient's choice, distribution of disease and local availability, bioassays comparing vehicles and corticoid molecules have demonstrated that ointments are the most effective, followed by creams and lotions. A recent study with clobetasol has suggested that spray vehicle is slightly more efficacious than other vehicles. Besides the important role of specific factors involved in the formulation of the spray, this greater efficacy may be due to increased patient compliance with an odourless, easy to apply, low residue, and elegant vehicle.

Excipients could play a role in the penetrance of the active substance and hence have an influence on efficacy and safety. The composition of the products used in the published clinical studies and the product applied for has been compared. The qualitative and quantitative compositions for Eczoria and Clovate was demonstrated to be similar.

IV.3 Pharmacodynamics

The pharmacodynamics of corticosteroids is well known and described in the scientific literature. The MAH has provided a brief overview of the anti-inflammatory, immunosuppressive, antiproliferative and vasoconstrictive effects of topical corticosteroids (Pels et al 2008; Gordon 1998).

IV.4 Clinical efficacy

The indications applied for are similar to the authorised therapeutic indications for medicinal products with the same active substance which are the following:

- Psoriasis (excluding plaque psoriasis)
- Recalcitrant eczema
- Lichen planus
- Discoid lupus erythematosus and other skin conditions that do not respond satisfactorily to less active steroids.

In the clinical overview the MAH has provided an overview of the epidemiology pathology, clinical presentation and current treatment modalities for each of the following conditions: Psoriasis (Mitra 2010), lichen planus (Wagner et al 2013) discoid lupus erythematosus or lupus erythematosus, recalcitrant eczema (atopic dermatitis) (Hanifin and Reed 2007; Spergel 2010). Internet sources were also used.

The MAH has provided an extended overview of the literature and discussed publications referring to clinical data on the use of clobetasol propionate (different concentrations in some cases) or other level IV corticosteroids in the above mentioned indications.

The majority of the supporting literature is related to the treatment of plaque psoriasis in which a large amount of data has been generated and published. In addition studies in severe chronic eczema, lichen planus and cutaneous lupus erythematosus are provided. The list of references is extensive and up to date. It includes publications from the 80's up to a Cochrane review (Mason et al 2013) on treatment of plaque psoriasis (Analysis 8.1, 8.3, 8.4).

With regard to clinical treatment guidelines the following have been referred to:

Treatment of psoriasis
European S3-Guidelines on the systemic treatment of psoriasis vulgaris.
Guidelines of care for the management and treatment of psoriasis with topical therapies (Nast et al. 2012, Pathirana et al. 2009, Murphy 2011).

American Academy of Dermatology Guidelines of care for the management of psoriasis and psoriatic arthritis (Menter et al. 2009).

Treatment of eczema
The efficacy of '0.05% Clobetasol + 2.5% zinc sulphate' cream vs. '0.05% Clobetasol alone' cream in the treatment of the chronic hand eczema is compared in a double-blind study (Faghihi et al. 2008). Additional data on treatment practices of hand eczema are provided in Soost et al (2011).

Treatment of lichen planus
Efficacy is supported by clinical study data. Radfar et al (2008) present data from a comparative treatment study of topical tacrolimus and clobetasol in oral lichen planus. The general clinical practice for lichen planus is discussed in a review in the New England Journal (Le Cleach and Chosidow, 2012). Clinical practice in children is also discussed (Balasubramaniam et al, 2008; Pandhi et al, 2013).

Treatment of lupus erythematodes
Efficacy of tacrolimus vs. clobetasol propionate in the treatment of facial cutaneous lupus erythematosus (data from a randomized, double blind, bilateral comparison study) is presented in Tzung et al (2007) and in therapy-resistant cutaneous lupus erythematosus: a cohort study (Madan et al 2009.

IV.5 Clinical safety

A review of safety data has been provided. The discussion refers mainly to clobetasol propionate 0.5 mg/g cream which was approved in Spain in December 1981 (Clovate) and other topical drugs approved with the same active ingredient, in the same or different pharmaceutical forms.

Arguments for an acceptable safety profile are that no actions have been taken for withdrawal, rejection, suspension or failure to obtain a renewal of a marketing authorisation related to safety signals/concerns. The safety profile is discussed with focus on the most common adverse events, namely skin disorders (including psoriasis, skin atrophy and pruritus without inflammation), local hypersensitivity reactions, eye disorders (increased risk of glaucoma and/or cataract if applied on eyelids), opportunistic infections (including bacterial, fungal, viral cutaneous infections), potential risks when used in chronic leg ulcers, skin atrophy and striae, resulting from prolonged use (Gordon 1998; Murphy 2011).
Manifestations of hypercortisolism (including Hypothalamo-Pituitary-Adrenal (HPA) axis suppression and Cushing's syndrome), which is a rare but very serious adverse events has been discussed as well and in particular the safety concerns related to use in children (Harris and Hunter 1988; Jorizzo et al 1997).

IV.6 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 Eczoria.

- Summary table of safety concerns as approved in RMP

Important identified risks	• Local hypersensitivity reactions (mainly related to excipients) • Skin disorders (including local skin atrophy and generalised pustular psoriasis) • Hypercortisolism (including Hypothalamopituitary-adrenal (HPA) axis suppression and Cushing´s syndrome)

	• Eye disorders: increased risk of glaucoma. • Opportunistic infections (including bacterial, fungal, viral cutaneous infections)
Important potential risks	None
Missing information	• Use in pregnancy • Use in lactation • Use in children under 1 year

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.7 Discussion on the clinical aspects

The provided literature is considered sufficient to support that clobetasol propionate is well established in the indications applied for. The clinical overview on the clinical pharmacology, efficacy and safety is adequate. The efficacy of clobetasol propionate in the treatment of the four indications is adequately demonstrated. For each indication reference has been made to publications describing the disease and current treatment options. The safety profile of clobetasol propionate 0.5% for topical use is well known and the risks are covered in the corresponding sections of the SmPC.

The MAH has adequately shown that the qualitative and quantitative composition and physical-chemical properties of Eczoria and the reference product Clovate are similar, and that literature data can be bridged to the product of this application. Risk management is adequately addressed.

V. USER CONSULTATION

The package leaflet (PL) 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 test consisted of a pilot test with 4 participants, followed by two rounds with 10 participants each. The questionnaires in the first and the second round included 19 specific questions about the product and about the format of the leaflet. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.
In both rounds a 100% score as reached with regard to finding the right location in the leaflet and giving the right answer to the questions.
The results show 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.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Eczoria 0.5 mg/g cream has a proven chemical-pharmaceutical quality. The use of the active substance is considered well-established for treatment of psoriasis (excluding plaque psoriasis), recalcitrant eczema, lichen planus, and discoid lupus erythematosus and other skin conditions that do not respond satisfactorily to less active steroids.

Clobetasol propionate cream has a favourable efficacy and safety profile. Adequate non-clinical and clinical literature data have been provided.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states considered that well-established use has been demonstrated for Eczoria and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 27 October 2016.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached

Literature references

Balasubramaniam P, Ogboli M, Moss C. Lichen planus in children: review of 26 cases. Clin Exp Dermatol. Jul 2008;33(4):457-9

Faghihi G, Iraji F, Shahingohar A, Saidat A. The efficacy of '0.05% Clobetasol + 2.5% zinc sulphate' cream vs. '0.05% Clobetasol alone' cream in the treatment of the chronic hand eczema: a double-blind study. J Eur Acad Dermatol Venereol. 2008 May;22(5):531-6. Epub 2008 Feb 12.

Gordon ML. The role of clobetasol propionate emollient 0.05% in the treatment of patients with dry, scaly, corticosteroid-responsive dermatoses. Clin Ther. 1998 Jan-Feb;20(1):26-39.

Hanifin JM, Reed ML; Eczema Prevalence and Impact Working Group. A population-based survey of eczema prevalence in the United States. Dermatitis.2007 Jun;18(2):82-91. PubMed PMID: 17498413.

Harris DW, Hunter JA. The use and abuse of 0.05 per cent clobetasol propionate in dermatology. Dermatol Clin. 1988 Oct;6(4):643-7.

Jorizzo JL, Magee K, Stewart DM, et al. Clobetasol propionate emollient 0,05 percent: Hypothalamic-pituitary-adrenal axis safety and four week clinical efficacy results in plaque-type psoriasis. Cutis. 1997;60:55-60.

Le Cleach L, Chosidow O. Clinical practice. Lichen planus. N Engl J Med. 2012 Feb 23;366(8):723-32. doi: 10.1056/NEJMcp1103641. Review. PubMed PMID: 22356325.

Madan V, August PJ, Chalmers RJ. Efficacy of topical tacrolimus 0.3% in clobetasol propionate 0.05% ointment in therapy-resistant cutaneous lupus erythematosus: a cohort study. Clin Exp Dermatol. 2010 Jan;35(1):27-30. Epub 2009 Jun 22.

Mason AR, Mason J, Cork M, Dooley G, Hancock H. Topical treatment for chronic plaque psoriasis (Review). Cochrane Database Syst Rev. 2013 Mar 28;3:CD005028.

Menter A, Korman NJ, Elmets CA et al. American Academy of Dermatology Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 3. Guidelines of care for the management and treatment of psoriasis with topical therapies. J Am Acad Dermatol 2009; 60: 643–659.

Mitra A, Wu Y. Topical delivery for the treatment of psoriasis. Expert Opin Drug Deliv. 2010 Aug;7(8):977-92.

Murphy G, Reich K. In touch with psoriasis: topical treatments and current guidelines. J Eur Acad Dermatol Venereol. 2011 Jun;25 Suppl 4:3-8.

Nast A, Boehncke WH, Mrowietz U et al. German S3 guidelines on the treatment of Psoriasis vulgaris (short version). Arch Dermatol Res 2012 Mar;304(2):87-113.

Pandhi D, Singal A, Bhattacharya SN. Lichen planus in childhood: a series of 316 patients. Pediatr Dermatol. 2014 Jan-Feb;31(1): 59-67. doi: 10.1111/pde.12155.Epub 2013 Apr 29. PubMed PMID: 23627802

Pathirana et al. JEADV October 2009, volume 23, supplement 2 European S3-Guidelines on the systemic treatment of psoriasis vulgaris.

Pels R, Sterry W, Lademann J. Clobetasol propionate--where, when, why? Drugs Today (Barc). 2008 Jul;44(7):547-57.

Radfar L, Wild RC, Suresh L. A comparative treatment study of topical tacrolimus and clobetasol in oral lichen planus. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2008 Feb;105(2):187-93.

Soost S, Abdollahnia M, Kostev K, Worm M Topical therapy of hand eczema - analysis of the prescription profile from dermatologists in private practice. J Dtsch Dermatol Ges. 2011 Sep 17.

Spergel JM. Epidemiology of atopic dermatitis and atopic march in children. Immunol Allergy Clin North Am. 2010 Aug;30(3):269-80. doi:10.1016/j.iac.2010.06.003. Review. PubMed PMID: 20670812

Tzung TY, Liu YS, Chang HW. Tacrolimus vs. clobetasol propionate in the treatment of facial cutaneous lupus erythematosus: a randomized, doubleblind, bilateral comparison study. Br J Dermatol. 2007 Jan;156(1):191-2

Wagner G, Rose C, Sachse MM. Clinical variants of lichen planus. J Dtsch Dermatol Ges. 2013 Apr;11(4):309-19. doi: 10.1111/ddg.12031. Epub 2013 Jan 15. Review. PubMed PMID: 23320493.)