CBG MEB

# Public Assessment Report

# Scientific discussion

# Betamethasone Exeltis 1 mg/g cutaneous solution

# (betamethasone valerate)

## NL/H/3554/001/DC

## Date: 19 April 2018

**This module reflects the scientific discussion for the approval of Betamethasone Exeltis 1 mg/g cutaneous solution. The procedure was finalised on 14 December 2016. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.**

## List of abbreviations

| | |
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| 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 Betamethasone Exeltis 1 mg/g cutaneous solution, from Exeltis Healthcare S.L.

The product is used for the treatment of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses of the scalp, such as psoriasis.

Betamethasone Exeltis 1 mg/g cutaneous solution is indicated in adults and children over 1 year of age.

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

Marketing authorisations for betamethasone applications have been issued in the EEA since decades. Exeltis Healthcare S.L. has developed a cutaneous solution containing 1 mg/g betamethasone.

The concerned member states (CMS) involved in this procedure were Germany, Hungary and Poland.

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC, a so called bibliographic application based on the well-established medicinal use of betamethasone.

# II. QUALITY ASPECTS

## II.1 Introduction

Betamethasone Exeltis is a colourless, cloudy slightly viscous cutaneous solution.

Each gram of the solution contains 1 mg of betamethasone, as 1.22 mg betamethasone valerate.

The product is packed in HDPE bottles with LDPE plug and HDPE screw caps.

The excipients are carbomer 980, isopropyl alcohol, sodium hydroxide (for pH adjustment) and purified water.

## II.2 Drug Substance

The active substance is betamethasone valerate, a well established active substance described in the European Pharmacopoeia (Ph.Eur.). Betamethasone valerate is a white or almost white, odourless crystalline powder practically insoluble in water, freely soluble in acetone and in methylene chloride, soluble in ethanol (96%).

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 Ph.Eur.

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

Quality control of drug substance
The active substance specification is considered adequate to control the quality. The specification meets the requirements of the monograph in the Ph.Eur. and includes additional testing specified in the CEP and additional tests for particle size distribution. Absence of a test for microbiological purity

has been adequately justified. Batch analytical data demonstrating compliance with this specification have been provided for sufficient batches.

Stability of drug substance
The active substance is stable for five years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

## II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The excipients are well known, commonly used in the manufacture of medicinal products intended for cutaneous use and of Ph.Eur. quality. A compatibility study has been carried out. Furthermore information on the formation of related substances in a forced degradation study has been provided. This data together with the stability study results confirm that no other degradation products except for those identified during the forced degradation study are formed. This is considered sufficient information with respect to compatibility of the active substance and excipients. The pharmaceutical development has been adequately performed.

Manufacturing process
The whole process of obtaining the finished product comprises of five stages. A flow diagram and narrative description of the manufacturing process as well as an overview of the equipment required for the manufacturing have been provided. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three industrial scale batches in accordance with the relevant European guidelines. Furthermore the revalidation taking into consideration additional parameters test, such as viscosity, surface tension and revised impurity specification has been performed on the three industrial scale batches.

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

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identification, assay, pH, density, viscosity, surface tension, related substances and microbiological control. The claimed limits for two specified impurities and total impurities are different at release and at the end of shelf life. For all other tests the limits at release and at the end of shelf life are identical.

Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Batch analyses data for the several batches has been provided. Some batches comply with the proposed specification, other have out of specification results for impurities. Information on degradation pathways of the drug product has been provided. The proposed limits for specified and unspecified impurities are acceptable.

Microbiological attributes
The MAH has demonstrated that the methods described in the Ph.Eur. are suitable for the microbiological control of the product Betamethasone Exeltis 1 mg/g cutaneous solution. The performed tests and the obtained results have been sufficiently provided.

Stability of drug product
Stability studies have been performed in accordance with ICH guideline. Stability data on the product have been provided for three industrial batches of each presentation in accordance with applicable European Guidelines. Batches were stored up to 24 months at long-term (25°C/60% RH), 24 months at intermediate (30°C/65% RH) and 6 months at accelerated conditions (40°C/75% RH). Out of specification results are obtained at 40°C/75% RH, regarding impurity levels. Results at intermediate conditions of 30°C/65% RH are within specification up to 12 months. A shelf-life of 24 months is acceptable with the storage condition ‘Store below 30°C’.

It has been demonstrated that the weight loss remains below 5% for both drug product presentations

(30 g and 60 g) throughout the shelf-life. Based on a provided photostability study it has been concluded that Betamethasone Exeltis 1 mg/g cutaneous solution in immediate packaging is stable when exposed to light.

Results of an in-use stability study have been provided for the 30 g product and 60 g product. The results justify for the 60 gram product an in-use period of 3 months and for the 30 gram product an in-use period of one month.

Specific measures concerning 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 Betamethasone Exeltis 1 mg/g cutaneous solution has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made.

- The MAH committed to provide the stability study results for three industrial scale batches as soon as available on demand of the MEB. The studies will be performed according to the approved, updated protocol, including the approved parameters, analytical methods and shelf-life limits.
- The MAH committed to perform stability studies also at 25°C/40% RH for confirmation of weight loss.

## III. NON-CLINICAL ASPECTS

### III.1 Pharmacology

Betamethasone valerate is the 17-valerate ester of betamethasone, a synthetic glucocorticoid with metabolic, immunosuppressive and anti-inflammatory actions. Betamethasone valerate binds to specific intracellular glucocorticoid receptors and subsequently binds to DNA to modify gene expression. The synthesis of anti-inflammatory proteins is induced while the synthesis of inflammatory mediators is inhibited. As a result, there is an overall reduction in chronic inflammation and autoimmune reactions.

### III.2 Pharmacokinetics

For the application, betamethasone valerate is used topically. Topical corticosteroids can be systemically absorbed from intact healthy skin. The extent of percutaneous absorption of topical corticosteroids is determined by many factors, including the vehicle and the integrity of the epidermal barrier. Occlusion, inflammation and/or other disease processes in the skin may also increase percutaneous absorption. However, systemic exposure to topical corticosteroids is expected to be very low. If systemic absorption does occur, betamethasone valerate is transported to the liver where betamethasone 21-valerate rapidly undergoes enzymatic hydrolysis to the free alcohol form of betamethasone, which is further metabolised and inactivated as a glucocorticoid. Corticosteroids are metabolised, primarily in the liver and are excreted by the kidneys, with some metabolites being excreted through bile.

### III.3 Toxicology

*Repeat-dose toxicity*
Repeat-dose toxicity of betamethasone valerate has been evaluated following systemic administration (oral and intraperitoneal) of betamethasone valerate to rats and dogs (0.25-3 mg/kg/day) for up to six weeks and subcutaneous administration for up to 6 months in rats (0.08–3 mg/kg/day). Systemic findings consistent with glucocorticoid toxicity were observed after oral, intraperitoneal or subcutaneous administration. Administration of betamethasone valerate at dose levels as low as 0.08

mg/kg/day subcutaneously resulted in changes in haematology and clinical chemistry parameters as well as decreases in body and organ weights. Repeat topical applications of 0.12% betamethasone valerate cream or ointment formulations have been studied. In rats administered 1.5 g/kg/day, ointment or cream (0.12% betamethasone valerate) for 6 months resulted in significant systemic effects characteristic of glucocorticoids, including suppression of weight gain, adrenal and thymic atrophy, lymphopenia, and fat/glycogen deposition in the liver. Similar findings, with less severity, were seen in dogs and rats treated topically for 90 or 30 days, with doses of 200 or 250 mg/kg/day ointment (0.12% betamethasone valerate), respectively. These effects were largely reversible upon cessation of exposure to betamethasone valerate. At low doses, and shorter time periods, side effects from topical administration of betamethasone valerate were minimal or non-existent

The following adverse effects have been noted with therapeutic use of betamethasone valerate in humans: changes in clinical chemistry parameters; suppression of adrenal glands; increased susceptibility to infection; symptoms of hypersensitivity (such as skin rash, hives, itching, and difficulty breathing).

*Genotoxicity*
Betamethasone was found to be genotoxic in the *in vitro* human peripheral blood lymphocyte chromosome aberration assay with metabolic activation and in the *in vivo* mouse bone marrow micronucleus assay.

*Carcinogenicity*
Long-term animal studies to determine the carcinogenicity of topical corticosteroids have not been done. Betamethasone valerate is not part of the International Agency for Research on Cancer (IARC) list of carcinogens.

*Reproductive and developmental toxicity*
Effects on embryo-foetal development have been reported in various laboratory animal species treated topically or subcutaneously with betamethasone valerate. Foetal effects, including decreased body weight gain, foetal resorption, skeletal defects including cleft palate, and death have been reported with varying severity with dose levels between of 0.1-0.625 mg/kg/day in rabbits treated subcutaneously or topically with betamethasone valerate during gestational days (GD) 6/7 to 18. Subcutaneously administration of betamethasone valerate to rats resulted in decreased foetal body weights at a dose level of 0.1 mg/kg/day, and skeletal malformations starting at a dose level of 1 mg/kg/day. Skeletal malformations have been reported in rats from topical administration of betamethasone valerate at 1.8 mg/kg/day (dosing period not specified). These results are similar to those of other corticosteroids. Subcutaneous administration of betamethasone valerate to mice or rats at doses ≥0.1 mg/kg/day or rabbits at doses ≥12 µg/kg/day during pregnancy produced foetal abnormalities including cleft palate.

*Local tolerance*
Mild irritation was observed after 14 days repeated exposure of 0.1% betamethasone cream in rabbits. In a comparative skin and eye irritation study with multiple corticosteroids in rabbits, no skin and eye primary irritations except minimal skin erythema and slight conjunctival redness were seen.

*Excipients*
The reported excipients for the formulation have proved to be safe in solid and semisolid formulations.

### III.4 Ecotoxicity/environmental risk assessment (ERA)

Since Betamethasone Exeltis is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

### III.5 Discussion on the non-clinical aspects

The application for Betamethasone Exeltis 1 mg/g cutaneous solution is based on well-established use. This is endorsed, since betamethasone has been registered for this indication for a long time and the dose is not increased. 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.

# IV. CLINICAL ASPECTS

## IV.1 Introduction

Betamethasone is a well-known active substance with established efficacy and tolerability.
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. Therefore, the member states agreed that no further clinical studies are required.

## IV.2 Pharmacokinetics

Systemic absorption may occur, in particular if betamethasone is applied to large areas and under occlusive dressing. Bioavailability of 14% after topical application has been observed.

## IV.3 Pharmacodynamics

The MAH has sufficiently discussed the pharmacodynamics of topically administered betamethasone, including anti-inflammatory, anti-proliferative, vasoconstrictive, immunosuppressive and apoptotic and anti-apoptotic properties.

## IV.4 Clinical efficacy

The MAH has submitted a clinical overview describing the available bibliographic data on efficacy of betamethasone valerate in a number of skin conditions, dating from 1970s to 2010s. Only a few studies were provided concerning specifically dermatoses of the scalp.
In the majority of the studies in psoriasis, betamethasone was compared to another class III corticosteroid or vitamin D3 analogue calcipotriene, which is considered equal in effect to class III corticosteroid, without comparison to placebo. There is lack of demonstrating assay sensitivity. In two studies the comparator was as vehicle control, in which the advantage of betamethasone was demonstrated.
Scalp psoriasis is an acceptable indication for a high potency topical corticosteroid according to EMA guideline 'Clinical investigation of corticosteroids intended for use of the skin' (3CC26A). Therefore the efficacy of betamethasone valerate in the treatment of scalp psoriasis is considered demonstrated.

## IV.5 Clinical safety

The MAH has provided a discussion over the mechanisms behind most common adverse events of topical corticosteroids, and a short summary of safety observations from literature studies with betamethasone. Most common adverse events were local skin reactions. The clinical overview is considered sufficient.

## 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 Betamethasone Exeltis.

Summary table of safety concerns as approved in RMP:

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| Important identified risks | • Local hypersensitivity reactions (due to the active substance or the excipients)<br>• Skin disorders (including local skin atrophy, generalised pustular psoriasis and rebound relapse in psoriatic patients)<br>• Hypothalamo-pituitary-adrenal (HPA) axis |

| | |
|---|---|
| | suppression and Cushing's syndrome<br>• Eye disorders (increased risk of glaucoma and cataracts)<br>• Opportunistic infections (including bacterial, fungal and viral cutaneous infections) |
| Important potential risks | • Use in pregnancy (due to potential effects on the embryo: intra uterine growth retardation and decreased adrenal gland function) |
| Missing information | • Use in lactation<br>• 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

Betamethasone Exeltis 1 mg/g cutaneous solution is considered widely established. For this authorisation, reference is made to clinical studies and experience with betamethasone. Betamethasone has been shown to be effective in the treatment of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses of the scalp, such as psoriasis. No new clinical studies were conducted. This is accepted.

## 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, followed by two rounds with ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and PL of medicinal products for human use.

## VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Betamethasone Exeltis 1 mg/g cutaneous solution has a proven chemical-pharmaceutical quality. Betamethasone Exeltis is an effective drug, which is considered widely established. The benefit/risk balance is considered positive.

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, on the basis of the data submitted, considered that essential similarity has been demonstrated for Betamethasone Exeltis with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 14 December 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 |
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