LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Oviderm
(propylene glycol)

SE/H/1650/01/DC

This module reflects the scientific discussion for the approval of Oviderm. The procedure was finalised on 2017-07-06. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Galenica AB has applied for a marketing authorisation for Oviderm® 250mg/g cream. The active substance is propylene glycol. Propylene glycol has water-binding properties which result in a moisturizing effect.

For approved indications, see the Summary of Product Characteristics.

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

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83 and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Introduction

The non-clinical overview was written by Lars Wiklund, M.Sc, Senior Toxicologist at RegSafe – Regulatory Safety Sciences, Stocksund, Sweden, dated 18 October 2016. The non-clinical overview is considered adequate.

III.2 Pharmacology

Propylene glycol has humectant properties and is used similarly to glycerol in topical moisturizing preparations. It is used in a wide variety of pharmaceutical formulations as a solvent and vehicle, especially for drugs unstable or insoluble in water, as a stabilizer for vitamins, and in ointments for medicinal applications. The Applicant provided literature based data on pharmacology of propylene glycol, since this application is based on well-established use of the substance. This is considered appropriate.

III.3 Pharmacokinetics

The pharmacokinetics of propylene glycol is reasonably well understood in humans as well as animals. Data indicate rapid and extensive oral absorption followed by rapid distribution into total body water. The Applicant provided literature based data on pharmacokinetics of acetylsalicylic acid, since this application is based on well-established use of the substance. This is considered appropriate.

III.4 Toxicology

The Applicant provided literature based data on toxicology of propylene glycol, since this application is based on well-established use of the substance. This is considered appropriate. The toxicity of propylene glycol has been extensively reviewed, and its safety profile is well known from a long history of frequent use in pharmaceuticals, cosmetics and food. In addition, the toxicological/safety documentation for the excipients in the Propylene glycol 250 mg/g cream covers a wide range of end-points, and their toxicity and adverse reaction profiles are well known from many years of frequent use in pharmaceuticals, cosmetics and food. All the ingredients comply with EU and US legislation, and/or international pharmacopoeia standards, and all are accepted as pharmaceutical excipients.

No separate assessment report is prepared for the non-clinical module.

III.5 Ecotoxicity/environmental risk assessment

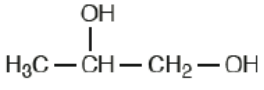
In accordance with Article 8(3) of Directive 2001/83/EC, as amended, the evaluation of the potential environmental risks posed by Oviderm should be submitted. The Applicant has submitted an appropriate justification for not performing ERA studies.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Oviderm 250 mg/g is a moisturizing cream intended for cutaneous use **(Figure 1).** The cream is an oil-in-water emulsion containing propylene glycol (propane-1,2-diol) with no other active compounds added.

Figure 1 Chemical structure of Propylene glycol



mw 76 g/mol

Absorption
Propylene glycol is rapidly absorbed from the GI-tract but also following topical application on damaged skin (1, 2).

Distribution
Propylene glycol seems to be widely distributed throughout the body (3).

Elimination
The half-life of propylene glycol is reported to be 5h, in neonates it is increased to 17h (4). The major elimination pathway for propylene glycol is hepatic metabolism *via* oxidation to lactic and pyruvic acids but it is also excreted unchanged in the urine (1, 2).

References
1. Handbook of pharmaceutical excipients 6th ed, editors Rowe RC, Sheskey PJ, Quin ME, 2009
2. Martindale 32nd ed, editor Parfitt K, 1999
3. Health effects of selected chemicals vol 2 p181, editor Mortensen B, 1993
4. American academy of paediatrics, Paediatrics 1997;99:268-78

IV.2 Pharmacodynamics

No pharmacodynamics studies have been performed with Propylene glycol 250 mg/g cream which is accepted considering that propylene glycol is a well-known compound.

Propylene glycol has keratolytic and water-binding properties that is beneficial in the treatment of dry skin of different genesis. Some antimicrobial effect has been shown against certain bacteria and yeast fungae, in particular *Malassezia furfur* (Faergemann and Fredriksson 1980).

The cream base contains coconut oil and has a fat content of 20%. The cream base has emollient and protective properties.

At strength of 250 mg/g cream propylene glycol has sufficient preservative effect, thus the product proposed for marketing does not contain any preservatives.

IV.3 Clinical efficacy

No clinical efficacy studies have been performed with Oviderm 250 mg/g cream which is accepted since the composition of Oviderm is overall similar to the cream base of Ovixan® 1 mg/g cream containing mometasone furoate as active ingredient, which received market authorization in 2012. Sweden was the RMS also for Ovixan.

The clinical experience with topical formulations containing propylene glycol is extensive.

Oviderm can either be used as a moisturizing cream for treatment of dry skin only, or in combination with corticosteroid treatment in skin disorders characterized with xerosis. Moisturizers are the basic treatment in both atopic dermatitis and psoriasis. Frequent use of moisturizers can increase disease free periods in patients with atopic dermatitis and improve skin barrier function, although the mechanism for the barrier improving effects is not fully understood. Use of a moisturizing cream can also reduce the risk of relapse of atopic dermatitis to approximately one third of that of no treatment (Wiren et al 2009).

There are a number of moisturizing creams on the Swedish market since the individual preferences do differ. Since consumer acceptance and patient compliance to a moisturizing cream is essential in treatment of dry skin of different genesis, a wide range of products on the market are considered beneficial for the patient/consumer.

IV.4 Clinical safety

The Applicant has in support of the application submitted a short review of safety of propylene glycol with respect to oral dosing, local side effects and systemic side effects following topical administration.

The Applicants conclusions that “Local application of dermal products containing propylene glycol in concentrations up to 25% is well tolerated and does not cause local irritation. Higher concentrations may produce irritant reactions. “Allergy to propylene glycol may develop and allergic reactions in subjects allergic to propylene glycol have been reported”, is overall endorsed.
The clinical experience with topical application of propylene glycol is extensive. Furthermore, the composition of Oviderm is qualitatively, but not quantitatively, the same as in the cream base or vehicle of Ovixan 1 mg/g cream, containing mometasone furoate as active ingredient. The results of the clinical efficacy and safety study with Ovixan did not indicate any safety concerns with the vehicle.

The aim of the Applicant was to develop a formulation without preservatives. 25% of propylene glycol is needed in order to make the formulation preservative free. If the local irritating effect of propylene glycol is acceptable to the patient/consumer, a moisturizer containing 25% propylene glycol can be justified. The possibility of local reactions in the target population is assessed as low. However, if it happens, they will mostly be of mild to moderate intensity and will resolve upon cessation of treatment.

The Summary of Product Characteristics adequately reflects the safety profile of the product.

IV.5 Risk Management Plans

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 Oviderm.

No risks have been identified with Oviderm that could affect the benefit/risk of the product. Relevant warnings are inserted in the SmPC, therefore no safety specification is considered to be needed.

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 RMP is approved.

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 Swedish.

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

The benefit/risk ratio is considered positive and Oviderm 250mg/g, cream is recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83 in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The Mutual recognition/Decentralised procedure for Oviderm 250mg/g, cream, was positively finalised on 2017-07-06.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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