LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Luxera
(methyl aminolevulinate hydrochloride)

SE/H/1565/01/DC

This module reflects the scientific discussion for the approval of Luxera. The procedure was finalised on 2016-05-12. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Galderma Nordic AB has applied for a marketing authorisation for Luxera, 160 mg/g, cream. The active substance is methyl aminolevulinate hydrochloride. Luxera has the same composition and the same pharmaceutical form as Metvix, 160 mg/g, cream, approved in Sweden on 2001-06-15, with PhotoCure ASA, as marketing authorisation holder.

For approved indications, see the Summary of Product Characteristics.

The marketing authorisation has been granted pursuant to Article 10c 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

References are made to the already approved product Metvix.

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity. In animal studies, when high doses of MAL were administered by IV route during gestation, reproductive toxicity was observed. Findings included delayed ossification and slight modifications on ossification parameters in rabbits and a slightly longer gestation duration in rats. As a result, MAL should be avoided during pregnancy in humans. Carcinogenicity studies have not been performed with MAL.

III.2 Ecotoxicity/environmental risk assessment

The MAH has submitted an ERA with this application, but under the condition of informed consent no new studies are to be submitted or assessed. Thus, the ERA cannot be presented or assessed at this time. However, the MAH has a type II variation for Metvix under assessment (SE/H/266/01/II/46) in which the identical ERA has been submitted. The RMS will present and assess the ERA during this procedure.

IV. CLINICAL ASPECTS

IV.1 Introduction

The application for Luxera, 160 mg/g cream, is an informed consent application of the reference product Metvix. Hence, reference was made to the studies performed with Metvix and no clinical data were provided in the dossier.

IV.2 Pharmacokinetics

Reference was made to the already approved product Metvix.

IV.3 Pharmacodynamics

Reference was made to the already approved product Metvix.

IV.4 Clinical efficacy

For the clinical efficacy of Luxera, reference was also made to the already approved product Metvix. The applicant has chosen to only include one of the indications approved for Metvix, i.e. “Treatment of thin or non-hyperkeratotic and non-pigmented actinic keratoses (AKs) on the face and scalp when other therapies are considered less appropriate. Luxera is indicated in adults above 18 years of age“.

Furthermore, for Luxera only the option of using daylight activation for the photodynamic therapy is included in the posology section of the SmPC. For Metvix, the posology includes both the option to use conventional photodynamic therapy with red light lamp (c-PDT) or to use daylight. Non-inferiority of Metvix Daylight-PDT compared to conventional-PDT has been demonstrated in two clinical studies.

IV.5 Clinical safety

Reference was made to the already approved product Metvix. The Luxera product information texts are as similar as possible to the current approved Metvix texts, but includes only the relevant information concerning the actinic keratoses indication and daylight treatment procedure. The undesirable effects section of the texts (e.g. section 4.8 of the SmPC) includes, however, all data obtained from clinical studies irrespective of Metvix indications or treatment procedures (c-PDT and DL-PDT), since currently there is not enough experience with the daylight photodynamic therapy to differentiate undesirable effects between the treatment procedures. No new adverse reactions were reported in the two Phase III daylight studies compared to the already known undesirable effects reported with c-PDT Metvix treatment of actinic keratoses.

IV.6 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 Luxera.

A risk management plan (RMP) had not previously been submitted and approved for Metvix since this product was approved several years ago. Hence, to comply with current requirements, a RMP was included in the MAA for Luxera. Based on comments on the initially submitted RMP, the RMP was subsequently considered acceptable.

Safety specification

The following summary of the safety concerns in Module SVIII was submitted in the most recent RMP version (2.0):

Summary of safety concerns	
Important identified risks	Application site hypersensitivity reactions Angioedema Post application hypertension
Important potential risks	Recurrence of treated lesions when the product is used for the treatment of BCC and Bowen's disease Evolution of actinic keratosis into SCC Off-label use in other conditions (e.g. acne, warts) Severe application site reaction including reactions with photosensitizing medication or in patients with photodermatoses Nevous system disorders/ Cerebrovascular events
Missing information	Use in pregnancy Use in immunosuppressed patients Use in children or adolescents

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.

Conclusion

The RMP 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.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Metvix, procedure no; SE/H/0266/001/II/27. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The application for Luxera, 160 mg/g cream, is an informed consent application of the reference product Metvix. Luxera has the same composition and the same pharmaceutical form as Metvix, 160 mg/g cream, approved in Sweden on 2001-06-15 and subsequently approved via MRP in several countries. The CMS for this application are CMS also for Metvix (SE/H/266/01).

The applicant has chosen to only include one of the indications approved for Metvix and only the option of using daylight activation for the photodynamic therapy. This mode of administration was recently approved in a variation application for Metvix. Similar to Metvix, the benefit risk is deemed positive for the treatment of thin or non-hyperkeratotic and non-pigmented actinic keratoses (AKs) on the face and scalp when other therapies are considered less appropriate.

An RMP has not yet been approved for Metvix, but a RMP for Luxera based on a suggested RMP for Metvix was submitted and assessed within the current informed consent application. The RMP was considered acceptable.

The benefit-risk for Luxera, 160 mg/g cream, is positive and the application 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 Decentralised procedure for Luxera, 160 mg/g, cream, was positively finalised on 2016-05-12.

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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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