LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Etylmorfin Evolan
(ethylmorphine hydrochloride)

Asp no: 2017-1058

This module reflects the scientific discussion for the approval of Etylmorfin Evolan. The procedure was finalised on 2019-01-08. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Evolan Pharma AB has applied for a marketing authorisation for Etylmorfin Evolan Oral solution 2,5mg/ml. The active substance is ethylmorphine hydrochloride,
(Etylmorfin Evolan används för behandling av rethosta. Det aktiva ämnet etylmorfin verkar hostdämpande).

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

Ethylmorphine Evolan belongs to the pharmaco-therapeutic group of opium derivates and expectorants (ATC code: R05F A02) and contains the active substance ethylmorphine hydrochloride, also known as dionine and codethyline. The proposed antitussive product has been used in Sweden in the product Cocillana-etyfin with the same qualitative and quantitative

composition since the 1960s. There is not much non-clinical information included for ethylmorphine.

III.2 Pharmacology

The active substance ethylmorphine has a cough center suppressant effect/antitussive effect. Ethylmorphine belongs to the class of organic compounds known as morphinans and is similar in its chemical structure to morphine and codeine. The exact target location(s) of the molecular effects of ethylmorphine that lead to the antitussive effect remain unclear.

III.3 Pharmacokinetics

Only limited non-clinical pharmacokinetic data is available concerning ethylmorphine. There is no information regarding absorption, distribution or excretion of ethylmorphine in animals. Ethylmorphine is metabolised by N-demethylation (to norethylmorphine) and by O-deethylation (to morphine). The N-demethylation is catabolised by CYP3A and CYP2C11 whereas CYP2D6 is responsible of O-deethylation. Ethanol at high concentration is reported to inhibit the metabolism of ethylmorphine in rat hepatocytes. Given the well-established use of ethylmorphine, these limitations are acceptable.

III.4 Toxicology

Since the application for Etylmorfin Evolan is a well-established use application, the nonclinical overview has to be based on bibliographic data from the public domain. In the public domain, the available information on ethylmorphine is limited. Publications on the, to ethylmorphine, structurally similar codeine is more frequent and thus used as a surrogate. However, ethylmorphine as an anti-tussive agent in the same qualitative and quantitative composition as in the present application was first authorized in 1964 in Sweden. The safety profile of ethylmorphine is thus mainly supported of the extensive clinical experience that outweighs the incompleteness of the nonclinical data presented.

No preclinical or clinical reproductive and reproductive toxicity information is supplied but it is stated that ethylmorphine transfers in mothers' milk and that Etylmorfin Evolan therefore should not be used by breastfeeding women (proposed SmPC 4.6).

III.5 Ecotoxicity/environmental risk assessment

According to directive 2001/83/EC, bibliographic/well-established use applications are required to include an environmental risk assessment (ERA). In the first round of questions the applicant was asked to either provide an acceptable refined PEC_{SW} value or submit the necessary Phase II data. The applicant submitted a revised Environmental Risk Assessment in which sales and consumption data in Sweden were presented years 2012-2018. The data showed that the yearly sales were approximately constant or tended to decrease. It was agreed that the approval of Etylmorfin Evolan was not considered to significantly increase the environmental exposure of etylmorphine, and therefore an ERA was not requested.

III.6 Discussion on the non-clinical aspects

The safety profile of ethylmorphine is mainly supported of the extensive clinical experience that outweighs the incompleteness of the nonclinical data presented.

IV. CLINICAL ASPECTS

IV.1 Introduction

For an application according to Article 10a, (well established medicinal use, WEU) the applicant needs to demonstrate that the active substance of the medicinal product has been in

well-established medicinal use for the claimed therapeutic indication within the Union for at least ten years, with recognised efficacy and an acceptable level of safety.

IV.2 Pharmacokinetics

The supporting information on PK, efficacy and safety for Etylmorfin Evolan is based on literature data on different products containing ethylmorphine.

Ethylmorphine has a fast absorption with a tmax of about 45 minutes and a fast elimination with a half-life of about 2 hours. Ethylmorphine is vastly metabolised via CYP3A and CYP2D6 through three different pathways, namely 6- glucuronidation to ethylmorphine-6-glucuronide, 0-deethylation to morphine and N-demethylation to norethylmorphine. Approximately 77% of the dose of ethylmorphine is found as parent and metabolites in urine samples.

IV.3 Pharmacodynamics

Opioids such as ethylmorphine are centrally-acting antitussive drugs. Ethylmorphine is considered to have the same mechanism of action presented for its analogues morphine and codeine. Comparable to codeine, ethylmorphine is metabolised to morphine in humans. The primary action of codeine and ethylmorphine is on the central cough pathway. It is accepted that the exact mechanism of action for narcotic antitussives is currently not known.

IV.4 Clinical efficacy

Provided bibliographic data is primarily based on textbooks of recognized scientific relevance, as well as on original articles. Most of the references used have been identified by a search performed within the clinical databases up to July 2017. Several commercial brands of ethylmorphine syrups against cough exist in the EU market, for example Cocillana Etyfin, approved in Sweden since 1964.
Overall, the applicant has presented bibliographic data which supports well-established medicinal use (WEU) of ethylmorphine for oral use in the short-term treatment of cough according to Article 10a of Directive 2001/83/EC.

IV.5 Clinical safety

The adverse events profile of ethylmorphine, being an opiate, is considered well established. Ethylmorphine gives classical opiate symptoms including miosis, respiratory- and CNS-depression. Significant toxicity occurs at overdose and children are particularly vulnerable.

Ethylmorphine is as other opioids classified as a narcotic substance and there is a risk for misuse and abuse. The SmPC clearly states that long-term use should be avoided.

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 Etylmorfin Evolan.

Safety specification

Important identified risks	None
Important potential risks	None
Missing information	Use in pregnancy

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The MAH has satisfactory responded to the questions raised and updated the RMP accordingly.
The submitted Risk Management Plan, version 2.0 signed 25 Jul 2018 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 MPA;
- 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

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 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

Benefits
Ethylmorphine is a centrally-acting antitussive drug, considered to have the same mechanism of action as its analogues morphine and codeine. Several commercial brands of ethylmorphine syrups against cough exist in the EU market, for example Cocillana Etyfin, approved in Sweden since 1964. Despite the very limited bibliographic efficacy information provided by the applicant, it is agreed that ethylmorphine containing medicinal products has a longstanding medicinal use for more than ten years in the EU and this important criterion for a WEU-application is thus considered fulfilled.

The WEU-criteria regarding the time over which a substance has been used with regular application in patients; quantitative aspects of the use of the substance, taking into account the extent to which the substance has been used in practice, the extent of use on a geographical basis and the extent to which the use of the substance has been monitored by pharmacovigilance or other methods are also considered supported, mainly based on information from ten approved products. Most referred products are approved in EU countries, one product is from Australia and two are from Norway. Nine of the medicinal products are indicated for use in cases of cough. The tenth product is indicated for respiratory tract infections, which could include cough as a symptom. Recommended maximal dose of ethylmorphine, for adults, are in the range of 24 mg–100 mg/day. Five products recommend 60–87.6 mg ethylmorphine daily. Overall, it is considered that WEU has been shown for ethylmorphine indicated for cough, from the age of > 2 years.

Risks

The adverse events profile of ethylmorphine, being an opiate, is considered well established. Ethylmorphine gives classical opiate symptoms including miosis, respiratory- and CNS-depression. Significant toxicity occurs at overdose and children are particularly vulnerable. Use in the adult population and adolescents is considered acceptable, but the use of opiates in children are currently being examined and it is noted that EMA initiated a review of codeine when used for cough and cold in children under Article 31 of Directive 2001/83/EC.
The treatment recommendations vary between products, not for long-term treatment, a few days, as short as possible. It can be concluded that use is symptomatic and for short term. No support for long-term treatment is found.

As ethylmorphine is a narcotic substance there is a need to mitigate misuse and abuse. The SmPC clearly states that long-term use should be avoided. Hence it is appropriate to restrict the package size to an amount corresponding to one course of treatment. A 1000 ml bottle is thus not approvable, which is accepted by the applicant.

Cocillana-Etyfin is classified as a narcotic medication in Sweden; this will apply also for Ethylmorphine Evolan if approval is granted.

The benefit/risk balance is considered positive for short-term use of Etylmorfin Evolan in the treatment of “rethosta” (irritating cough).

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

Etylmorfin Evolan Oral solution 2,5mg/ml was approved in the national procedure on 2019-01-08.

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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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