LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Cocifin
(ethylmorphine hydrochloride)

Asp no: 2021-0184

This module reflects the scientific discussion for the approval of Cocifin. The procedure was finalised on 2022-05-25. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Cocifin, 2,0 mg/ml, Oral solution.

The active substance is ethylmorphine hydrochloride (dihydrate), ethylmorphine. A comprehensive description of the indication and posology is given in the SmPC.

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

The application for Cocifin, 2,5 mg/ml, Oral solution, is submitted according to Article 10a of Directive 2001/83/EC (so called "well established use"; WEU). The applicant, Unimedic Pharma AB, applies for a marketing authorisation in Sweden through a National Procedure.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

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

This public assessment report is based on literature data. Only limited non-clinical literature is available for ethylmorphine and the non-clinical dossier uses therefore also literature on the structurally similar codeine and morphine (the latter a metabolite for both ethylmorphine and codeine). As ethylmorphine has been in well-established medicinal use for the sought indication within the EU for more than 10 years, the lack of specific ethylmorphine information is considered acceptable.

Pharmacology

The active substance ethylmorphine has a cough center suppressant effect/antitussive effect and belongs to the class morphinans (i.e., chemical substances that are similar in their chemical structure to morphine and codeine). The exact pharmacological mechanism of action for ethylmorphine (and morphine and codeine) as antitussives is not fully understood. It has been suggested that some of the metabolites of ethylmorphine (morphine, morphine-6-glucoronide and morphine-3-glucoronide) are the actual active metabolites which act as agonists to the μ-opioid receptor (a G-protein coupled receptor). Most of the information of likely pharmacological mechanism/mode of action for ethylmorphine are based on extrapolation of the results from studies on codeine and morphine (the main source of information in the provided non-clinical overview). Only a few dedicated ethylmorphine pharmacological studies have been reported. It can also be noted that that almost all of the reported in-vivo studies in which antitussive activity has been evaluated has been performed in animals with no underlying airway pathology. In an animal study, cough was induced in dogs via mechanical stimulation of the trachea. Ethylmorphine (alternatively codeine and morphine) was given intravenously. The minimal effective dose was defined as a dose “who gives a depressing effect visible on the cough curves and maintains it for about 20 minutes”. The estimated effective dose for ethylmorphine was 5mg/kg (compared to codeine at 3 mg/kg and morphine at 0.5 mg/kg). It has also been reported that ethylmorphine suppresses cough in guinea pigs that had been exposed to inhalation of sulphur dioxide. The ED50 for total suppression of the cough was at 13mg/kg (compared to 8mg/kg for codeine).

No ethylmorphine-specific safety pharmacology literature was submitted/found by the applicant. Instead, a number of studies involving codeine and morphine are listed. Codeine or morphine exposure in guinea pigs (i.v., at doses near the ED50 for antitussive action: morphine 1,5 mg/kg, codeine 10 mg/kg) generated a small (<20%), but significant depression of ventilation. It has been reported that both l-codeine and d-codeine affects the blood pressure and heart rate in cats when given in high doses (NOAEL 0,25 mg/kg iv i-codeine or 1,0 mg/kg i.v d-codeine).

Overall, it is clear that opioids such as ethylmorphine (and codeine and morphine) have a cough suppressant effect in animals but that the specific pharmacological mechanism of action remains uncertain.

Pharmacokinetics

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. Glucoronidation is responsible for the formation of the main metabolite ethylmorphine-6-glucoronide in a process mediated by UDP-glucuronosyltransferase 2B4 and 2B7. The three direct metabolites to ethylmorphine are (in humans): morphine, norethylmorphine and ethylmorphine-6-glucoronide (whereof morphine is an agonist to the μ-opioid receptor). Additional (believed) active metabolites in humans are morphine-6-glucoronide and morphine-3-glucoronide.

Toxicology

No toxicological literature for ethylmorphine has been provided. Non-clinical data considering genotoxicity, reproductive toxicity and carcinogenicity are generally the minimum requirement for WEU applications. No ethylmorphine data for these areas has been provided but the use of (mainly) codeine but also morphine information as surrogates is considered acceptable as ethylmorphine is partially metabolized to morphine and shares this same characteristic with codeine besides having very similar chemical structure and pharmacological profile.

Acute toxicity data in rat indicates a LD50 between 62mg/kg (intravenous exposure) and 810mg/kg (oral exposure). In the 2-week codeine dietary repeat-dose toxicity studies, the LOAEL (body weight reduction) was 1562 ppm (or 125 mg/kg) for rats and 3125 ppm for mice (female body weigh increase, male liver weight reduction; corresponding to 600-725 mg/kg). There was no NOAEL for rats while the NOAEL for mice was 1562 ppm (corresponding to 300-400 mg/kg). In 13-week studies, both mice and rats exhibited adverse effects already at the lowest given dose (LOAEL = 390 ppm). For rats, this corresponded to reduced body weight, increased adrenal weight, and reduced liver weight in males at around 25 mg/kg. In male mice, this corresponded to abnormal postures at 60 mg/kg. Leukocyte and lymphocyte depletion were found in rats from 1562 ppm (corresponding to 100 mg/kg) indicating a potential for immunotoxicity. The latter aspect is supported by a NTP study from 1992 with morphine where exposed mice demonstrated a decrease in spleen and thymus weights and several changes in immune cells. No toxicokinetics data is available for ethylmorphine or codeine. An estimation of repeat-dose toxicity human equivalent doses (HED) doses for codeine – and using the proposed ethylmorphine dosage – provided the following exposure margins (assuming a maximum intake of 40mL/day at 2.5mg/mL): 100mg/day corresponding to ~1.7mg/kg in a 60kg adult which gives a rough margin of around 12x (rat 2-weeks LOAEL of 20.2mg/kg) and 2.4x (rat 13-weeks LOAEL of 4mg/kg).

No genotoxicity or carcinogenicity data has been presented for ethylmorphine. Studies on the structurally similar codeine found that codeine, with and without S9 metabolic activation enzymes, induced dose-related increases in sister chromatid exchange in Chinese hamster ovary (CHO) cells at levels associated with cytotoxicity. Codeine was not mutagenic in any of four strains of Salmonella typhimurium, in the presence or absence of S9. It is therefore considered unlikely that ethylmorphine is mutagenic. It remains unclear whether morphine, the downstream metabolism product of both codeine and ethylmorphine is genotoxic. However, there was no evidence for carcinogenicity in rats and mice treated with codeine (see below). With regard to carcinogenicity, in rats, exposure to codeine via dietary administration for 2 years caused increased pituitary gland hyperplasia at 400 ppm (corresponding to 125 mg/kg) but not at higher doses. At the highest dose of 1600 ppm (corresponding to 450 mg/kg), an increase in preputial gland hyperplasia was found. The 2-year mouse codeine study found significantly greater incidence of thyroid gland follicular cell hyperplasia at 3000 ppm (corresponding to 400 mg/kg) in male mice after 15 months of exposure and in all dose groups after two years exposure (750, 1500 and 3000 ppm; corresponding to 100, 200 and 400 mg/kg respectively). Overall, no carcinogenic activity (i.e., neoplasms) could be found for codeine in either mice or rats and it is therefore considered unlikely that the structurally similar ethylmorphine is carcinogenic.

No information was available on reproductive toxicity for ethylmorphine. Literature on codeine and morphine indicate that ethylmorphine may influence the endocrine axis and reproductive organs in animal models. A 50% reduction in serum testosterone level was observed in male rats 4 hours after a single subcutaneous injection of 8,6 codeine/kg. Rats administered subcutaneous injections of morphine 50 mg/kg per day for up to 9 weeks showed decreased serum LH-hormone and testosterone levels and reduced seminal vesicle and prostate gland weight. These effects were reversed within the 13-week withdrawal period. The NOAELs for codeine’s prenatal exposure effects were 10mg/kg (hamsters) and 75mg/kg (mice) whereas the NOAELs for maternal toxicity were 50 (hamsters) and

150 (mice) mg/kg. In the high-dose hamster group (150mg/kg), meningoencephalocele (3% of foetus, 19% of litters) was found. The NOAEL and LOAEL (reduced foetal bodyweight) for hamster, 10 respectively 50 mg/kg, correspond to HED of 1.3 and 6.5 mg/kg. The HEDs for murine NOAEL and LOAEL (reduced foetal body weight), 75 and 150 mg/kg, are 6.1 and 12.2 mg/kg respectively. The possibility that ethylmorphine will pass over in human maternal milk has been noted in the proposed SmPC 4.6. text. No postnatal toxicity studies have been reported.

Overall, while the non-clinical information for ethylmorphine is limited, considering the WEU nature of the proposed product and the available data for the structurally and pharmacologically similar codeine and morphine, the limited non-clinical information provided is acceptable.

IV. CLINICAL ASPECTS

Pharmacokinetics
The supporting information on PK, efficacy and safety for ethylmorphine is based on literature data on different products containing ethylmorphine. In the literature studies supporting efficacy and safety mainly oral solutions of ethylmorphine has been used though no detailed information regarding excipients is available. The test product is an aqueous oral solution at time of administration and contains an active substance in the same concentration as an approved oral solution and does not contain excipients known to affect absorption; therefore, the bridge between the applied formulation and the formulations used in the literature to support efficacy and safety is from a pharmacokinetic perspective supported.

Following oral administration of ethylmorphine, maximum plasma concentrations are reached after about 1 hour. The plasma half-life is approximately 2 hours. Ethylmorphine is metabolised via N-demethylation to norethylmorphine and via O-deethylation to morphine, reactions catalysed by various forms of cytochrome P450 (CYP 2D6 and CYP 3A4). Ethylmorphine and its metabolites are mainly excreted by the kidneys in the form of conjugates with glucuronic acid. After 48 hours, approximately 70% of the administered dose was recovered in the urine.

If a patient is an ultra-fast metaboliser of CYP2D6, there is an increased risk of morphine-related side effects even at therapeutic doses. These patients rapidly convert ethylmorphine to morphine, which may result in higher-than-expected plasma levels of morphine.

Concomitant use of opioids and barbiturates, benzodiazepines, or other CNS depressants (such as other opioids, sedatives or hypnotics, general anaesthetics, phenothiazines, muscle relaxants, sedative antihistamines) increases the risk of sedation, respiratory depression, coma, and death due to CNS additives -depressive effect. The dosage and duration of concomitant use should be limited.

Since ethylmorphine is a well-known substance, the provided information is considered sufficient and supported by adequate references. The claims in the SmPC are acceptable.

Pharmacodynamics
Ethylmorphine likely exerts its effect by its active metabolites, by binding to opioid receptors in the cough center. The endogenous ligands for these receptors include the endorphins (μ), enkephalins (μ and d), the dynorphins (κ), and nociceptin/orphanin receptor. Opioids are believed to exert their effect on μ-receptors in the cough center.
The cough reflex is complex and not fully understood. The mechanism of opioids is neither fully understood. The available evidence indicates that opioids centrally act on opioid receptors located in the medulla oblongata. Nebulized codeine seems to have an effect on peripheral receptors in the airway, it is unknown whether opioids affect these receptors when administered via conventional routes.

Clinical efficacy
The applicant has presented 28 publications studies on antitussive effect of opiates published from 1938 to 2010. Most of the studies have evaluated use of codeine in cough. There are no assessable studies available specifically showing the effect of ethylmorphine as this compound has been approved since the 1960th and not investigated in published randomised trials. As ethylmorphine is metabolised to morphine which exerts the effect and morphine is the active compound also in case of codeine treatment the studies listed above were accepted as supportive to the application. Equipotency between ethylmorphine, codeine and morphine can nevertheless not be assumed and the posologies applied are thus not applicable. The posology proposed for Cocifin is in line with approved ethylmorphine-containing products on the market and thus found acceptable.

The applicant has also presented 3 publications on the use of opiates in children. All 3 studies concern the use of codeine as antitussive vs non-opiate antitussive treatments. The data provided indicates a similar efficacy profile in children as in adults. As for adults the data provided on codeine cannot be used to support the proposed posology in children but it was deemed acceptable to refer to other products approved.

Despite the very limited efficacy information provided by the applicant concerning the use of ethylmorphine as antitussive, 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 fulfilled. Overall, even though the included studies are not considered robust but justifiable to support the WEU-criteria regarding the degree of scientific interest in the use of the substance (reflected in the published scientific literature) and the coherence of scientific assessments and thus accepted as in line with WEU criteria.

In general, 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 considered supported with data for different approved products in EU. All referred products are approved in EU countries, and two are from Norway. Regarding the quantitative aspects of use, the MAH has presented exposure data of approved ethylmorphine containing products in Sweden and Norway which are included in the clinical safety section of the report. The quantitative aspects of use in two EU countries presented by the MAH are also in line with the WEU criteria.
Overall, the applicant has presented data which supports WEU of ethylmorphine for oral use in the short-term treatment of cough. Posologies recommended in the SmPC are in general in accordance with other ethylmorphine containing medicinal products in Sweden.

Clinical safety
The applicant has focused the safety part of their presentation on detailing the list of opioid class adverse events, overdose, and abuse of ethylmorphine as well as other opioids (i.e. codeine) used for cough indication in general. The safety profile of ethylmorphine, being an opiate, is considered well established. Ethylmorphine gives classical opiate symptoms including miosis, respiratory- and CNS-depression, gastro-intestinal disturbances, urinary tract retention, hormonal changes, sleep disturbances, cardiac- and haemodynamic effects as well as immune system effects. Tolerance is also a known complication for all opioids. High levels of morphine can lead to breathing difficulties which is of concern in case of overdose of ethylmorphine.

EMA initiated a review of codeine when used for cough and cold in children under Article 31 of Directive 2001/83/EC. The review was carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), which recommended that codeine should not be used in children below 12 years of age. In October 2019 the safety and development centre at Fimea restricted the use of ethylmorphine in Finland. Corresponding restrictions has not been deemed warranted in Sweden but risks related to dosing error and overdosing has been discussed recently. It is thus deemed acceptable to allow the age limit 2 years of age as detailed in Section 4.2 of the SmPC.

Ethylmorphine is as other opioids classified as a narcotic substance and there is a risk for misuse and abuse. To mitigate this risk the pack size of Cocifin is restricted to an amount corresponding to one course of treatment (maximum of 500 ml).

Pharmacovigilance system
The Applicant has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the MPA considers the Summary acceptable.

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 Cocifin.

Safety specification
There are no important risks or missing information listed in the RMP Part II: Module SVIII) which is appropriate considering the well-established use of the compound.

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 submitted Risk Management Plan, version 0.1 signed 2021-02-02 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

A user consultation with target patient groups on the package information leaflet has been performed on the basis of a bridging report making reference for content to Etylmorfin Evolan: 5.4.1-2017-73861 and for layout to D-vitamin Olja Unimedic: 5.4.1-2016-8440..
The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Well-established use
In order to approve a well-established use application, it needs to be shown that the active substance in the medicinal product has already been in medical use in the EU/EEA for at least ten years, and that its efficacy is recognised, and its level of safety is acceptable. The requirement to submit results of preclinical or clinical studies may be waived under certain conditions. In this case, studies will be replaced by the appropriate scientific literature.
Ethylmorphine containing medicinal products have a well-known and long-standing use for more than ten years in the EU countries and therefore this important criterion for a well-established use application is thus considered fulfilled.
In general, regarding the WEU criteria concerning the period of time over which a substance has been used with regular application in patients; the quantitative aspects of the drug consumption in clinical practice as well as the geographical extent of use and last but not the least the extent to which the ethylmorphine containing medicinal products have been monitored by means of pharmacovigilance are backed up mainly by the information provided from twelve approved products, all of which are approved in the EU countries. Ten out of these twelve ethyl morphine containing medicinal products are indicated to be use as antitussive against cough as a symptom and the two others are indicated for treatment of cough in the context of the respiratory tract infections. Ethylmorphine hydrochloride is recommended to children from 2 years. Paediatric posology based on weight and older is included in the SmPC of the Cocifin and information concerning dosing accuracy in children are also included in the SmPC of Cocifin in line with the other ethylmorphine containing medicinal products. Recommended maximum dose of ethylmorphine for adults are in the range of 45-120 mg/day. Overall, it is considered that WEU has been shown for ethylmorphine indicated for cough.

Benefits
Ethylmorphine is a centrally acting antitussive drug, considered to have the same mechanism of action as its analogues morphine and codeine. There are no assessable studies available specifically showing the effect of ethylmorphine as this compound has been approved since the 1960th and not investigated in published randomized trials. The applicant has presented 28 publications studies on antitussive effect of opiates published from 1938 to 2010 most of these conducted with codeine as the compound of investigation. As ethylmorphine is metabolised to morphine which exerts the effect and morphine is the active compound also in case of codeine treatment these studies are nevertheless accepted as supportive to the application. Equipotency between ethylmorphine, codeine and morphine can nevertheless not be assumed and the posologies applied are thus not applicable. The posology proposed for Cocifin is in line with approved ethylmorphine-containing products on the market and thus found acceptable. The applicant has also provided the posology for the children between 2-5 years of age in the SmPC of the product.

Risks
The safety profile of ethylmorphine, being an opiate, is considered well established. The adverse events listed includes classical opiate symptoms including miosis, respiratory- and CNS-depression, gastro-

intestinal disturbances, urinary tract retention, hormonal changes, sleep disturbances, cardiac- and haemodynamic effects as well as immune system effects. High levels of morphine can lead to breathing difficulties which is of concern in case of overdose of ethylmorphine.

Benefit/risk balance
From a quality, non-clinical and clinical point of view the application can be recommended for approval. Benefit/risk balance for Cocifin is considered positive.

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

N/A

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

N/A

VII. APPROVAL

Cocifin, 2,0 mg/ml, Oral solution was approved in the national procedure on 2022-05-25.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

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

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se