LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Morfin Alternova
(morphine hydrochloride)

Asp no: 2019-0413

This module reflects the scientific discussion for the approval of Morfin Alternova. The procedure was finalised on 2020-02-05. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Alternova A/S has applied for a marketing authorisation for Morfin Alternova, 5 mg, tablet. The active substance morphine hydrochloride is the same as in Morfin Alternova, tablet, marketed by Alternova A/S since 2014.

For approved indications, see the Summary of Product Characteristics.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83/EC 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

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology of morphine has been provided, which was based on scientific literature. Morphine is a widely used, well-known active substance and since this product has been shown to be essentially the same as the authorised Morfin Alternova, tablet (10mg, 20 mg), no further non-clinical data have been submitted or are considered necessary for this line-extension procedure.

III.1 Ecotoxicity/environmental risk assessment

Approval of Morfin Alternova, tablet 5 mg, is not expected to result in an increased exposure of the active substance to the environment since the product is intended as a substitute for other identical products on the market.

III.2 Conclusion on the non-clinical aspects

There are no objections to approval of Morfin Alternova from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

The application is based on a Biopharmaceutical Classification System (BCS) based biowaiver and no bioequivalence study has been submitted.

According to the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr), a BCS class I-based biowaiver is applicable for an immediate release product if the drug substance is not considered to have a narrow therapeutic index and has been proven to exhibit high solubility and complete absorption (BCS class I). Also, in-vitro dissolution characteristics of the test and the reference product should be either very rapid or similarly rapid and the excipients that might affect bioavailability should be quantitatively and qualitatively the same.

The conclusion for this line-extension application of the 5 mg strength is the same as for Morfin Alternova 10 mg and 20 mg. The applicant submitted a thorough justification regarding complete absorption of morphine that was considered sufficient to conclude that morphine can be classified as a BCS class I substance. Complete absorption could not be concluded based on data regarding absolute bioavailability, since morphine has a high first-pass effect. The main support of complete absorption was the submitted data showing that the amounts of morphine and glucuronide metabolites excreted in urine was very similar between iv and oral administration. The urine recovery rate was about 50-60 % the first 12 hours for both iv and oral administration. Data on absolute bioavailability of 101% (95% CI 56-147) from a study in patients with cirrhosis and severe liver dysfunction, in whom the hepatic metabolism is expected to play less role in biasing experimental data of *in vivo* intestinal permeation of morphine, was considered supportive. The applicant also submitted literature data regarding formulation effects that were considered supportive in showing that morphine has complete absorption.

The excipients are not identical in the test and reference product, but none of the excipients are

known to affect drug bioavailability.

Morphine is not considered to have a narrow therapeutic index.

Discussion and overall conclusion
In conclusion, the justification for a BCS (Biopharmaceutics Classification System) based biowaiver can be accepted for Morfin Alternova 5 mg, tablets.

The quality aspects for a BCS based biowaiver are also fulfilled.

IV.2 Risk Management Plans

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 Morfin Alternova, 5 mg, tablet.

Safety specification
Summary of safety concerns follows below.

Summary of safety concerns	
Important identified risks	Hypersensitivity reactions Aspiration/Secretion stagnation Respiratory depression Acute liver disease Use in patients in anxiety states during influence of alcohol or hypnotic medicines. Drug dependency Interactions with barbiturates, antacids, gabapentin Lactation
Important potential risks	Use in pregnancy Interactions with MAO-inhibitors
Missing information	Interaction between morphine and baclofen, benozodiazepin, hydroxoxizine, methylphenidate, nimodipine, ritonavir Fertility

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 1.3 signed 2018-06-15 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 (PIL) has been performed on the basis of a bridging report making reference to Morfin Alternova 10 and 20 mg tablets, Dnr. 5.4.1-2013-65192 and 5.4.1-2013-65193. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the medicinal product, Morfin Alternova is found adequate. There are no objections to approval of Morfin Alternova, from a non-clinical and clinical point of view. The product information is acceptable.

The application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC 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

Morfin Alternova, 5 mg, tablet was approved in the national procedure on 2020-02-05.

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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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