LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Morfin E Consult
(morphine hydrochloride)

Asp no: 2013-0732-33, 2014-0521-22

This module reflects the scientific discussion for the approval of Morfin E Consult. The procedure was finalised at 2014-06-19. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Morfin E Consult, 10 mg and 20 mg, tablet, are generic applications made according to Article 10(1) of Directive 2001/83/EC. The applicant, E Consult ApS, applies for a marketing authorisation in Sweden through a National Procedure.

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Morfin Meda, 10 mg, tablet authorised in SE since 1982, with Meda AB as marketing authorisation holder.

For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

The Morphine hydrochloride tablets are presented in the form of tablets containing 10 mg and 20 mg of morphine hydrochloride. The excipients are lactose monohydrate, maize starch, gelatine and magnesium stearate. The tablets are packed in PVC/aluminium blisters or HDPE-containers.

II.2 Drug Substance

Morphine hydrochloride has a monograph in the Ph Eur.

Morphine hydrochloride is a white, crystalline powder which is soluble in water, slightly soluble in ethanol (96%) and practically insoluble in toluene. The structure of the morphine hydrochloride has been adequately proven and its physico-chemical properties sufficiently described. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

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

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Morphine hydrochloride tablets are formulated using excipients described in the current Ph. Eur. The raw materials used in the product are of vegetable origin except gelatin and magnesium stearate.

All raw materials used in the product has demonstrated compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01).

The product development has taken into consideration the physico-chemical characteristics of the active substance.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

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 under ICH conditions have been performed and data presented support the shelf life claimed in the SPC with the storage condition “Do not store above 30 °C”.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

No bioequivalence study has been submitted since the applicant applies for a BCS class I based biowaiver. From a pharmacokinetic point of view, a BCS-class I based biowaiver is acceptable for an immediate release drug product if the drug substance has proven to exhibit complete absorption and the excipients that might affect bioavailability are quantitatively and qualitatively the same. It should also be confirmed that the substance is not a narrow therapeutic index drug.
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. Data on absolute bioavailability of 101% (95% CI 56-147) from a study in patients with cirrhosis and severe liver dysfunction were considered supportive. The applicant also submitted literature data regarding formulation effects that were considered supportive. Taken together, the justification submitted by the applicant regarding complete absorption was considered sufficient.

The excipients are not identical in the test and reference product, but none of the excipients are known to affect drug bioavailability.

The applicant also submitted a thorough justification based on an assessment of the therapeutic index of morphine in order to claim that morphine is not a narrow therapeutic index drug. The conclusion that therapeutic index of morphine is wide is acceptable.

In conclusion, a BCS-based biowaiver is acceptable from a pharmacokinetic and clinical perspective. The quality aspects for a BCS based biowaiver are also fulfilled.

The justification for BCS (Biopharmaceutics Classification System) based biowaiver can be accepted.

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

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.

The risk/benefit ratio is considered positive and Morfin E Consult is recommended for approval.

VI. APPROVAL

Morfin E Consult, 10 mg and 20 mg, tablet was approved in the national procedure on 2014-06-19.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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