LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Molterfin
(buprenorphine)

SE/H/928/01-03/DC

This module reflects the scientific discussion for the approval of Molterfin. The procedure was finalised at 2010-06-03. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

BMM Pharma AB has applied for a marketing authorisation for Molterfin, 0.4 mg, 2 mg and 8 mg sublingual tablets, claiming essential similarity to Subutex 0.4 mg, 2 mg and 8 mg sublingual tablets marketed in the EU by Schering Plough. The products contain buprenorphine hydrochloride as active substance. For approved indications see the Summary of Product Characteristics. The reference product used in the bio-equivalence study is Subutex 0.4 mg and 8 mg sublingual tablets marketed by Schering Plough in the UK.

II. QUALITY ASPECTS

II.1 Introduction

Molterfin are presented in the form of sublingual tablets containing 0.43 mg, 2.16 mg or 8.64 mg of buprenorphine hydrochloride which corresponds to 0.4 mg, 2 mg or 8 mg of buprenorphine. The excipients are for the 0.4 mg tablet citric acid, lactose monohydrate, magnesium stearate, maize starch, mannitol, povidone, colloidal anhydrous silica, sodium citrate and talc and for the 2 mg and 8 mg tablets citric acid, lactose monohydrate, magnesium stearate, maize starch, mannitol, povidone and sodium citrate. The sublingual tablets are packed in blisters.

II.2 Drug Substance

Buprenorphine hydrochloride has a monograph in the Ph Eur.

Buprenorphine hydrochloride is a white, or almost white crystalline powder which is sparingly soluble in water, freely soluble in methanol, soluble in ethanol (96 per cent) and practically insoluble in cyclohexane. The structure of buprenorphine hydrochloride has been adequately proven and its physico-chemical properties sufficiently described. No polymorphism was observed and the chirality of the drug substance is documented and supported. 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/degradation products 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

Molterfin, sublingual tablets are formulated using excipients described in the current Ph Eur. 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 no special storage precautions.

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

Absorption
When taken orally, buprenorphine undergoes pronounced first-pass hepatic metabolism with N-dealkylation and glucuroconjugation in the small intestine.
Per oral use of this medication is therefore inappropriate.
Peak plasma concentrations are achieved 90 minutes after sublingual administration and the maximal dose-concentration relationship is linear, between 2 mg and 16 mg.

Distribution
The absorption of buprenorphine is followed by a rapid distribution phase and a half-life of 2 to 5 hours.

Biotransformation
Buprenorphine is metabolised by 14-N-dealkylation and glucoroconjugation of the parent molecule and the dealkylated metabolite.
N-desalkyl-buprenorphine is an μ-agonist with intrinsic activity. Norbuprenorphine contributes to the overall pharmacological effect, however it is unknown to what extent.

Elimination
Elimination of buprenorphine is bi- or tri- exponential, with a long terminal elimination phase of 20 to 25 hours. This is in part due to re-absorption of buprenorphine after intestinal hydrolysis of the conjugated derivative, and in part due to the highly lipophilic nature of the molecule.

Buprenorphine is essentially eliminated in the faeces by biliary excretion of the glucuroconjugated metabolites (80 %). The residual 20 % is eliminated in the urine.

To support the application, the applicant has submitted two fasting single dose bioequivalence studies, one on the lowest strength 0.4 mg and one on the highest strength 8 mg and compared with respective strength of the reference product Subutex. Studies in fasting state are acceptable. Some questions were raised regarding the bioequivalence studies. All questions were satisfactorily answered and the product was recommended for approval from a pharmacokinetic point of view.

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 results of the conducted bioequivalence study can be extrapolated to other strengths (2 mg) since the criteria for biowaiver for additional strengths are fulfilled according to the Note for Guidance on the Investigation of Bioavailability and Bioequivalence.

The risk/benefit ratio is considered positive and the application for Molterfin, 0.4 mg, 2 mg and 8 mg sublingual tablets is recommended for approval.

VI. APPROVAL

The Decentralised procedure for Molterfin, 0.4 mg, 2 mg and 8 mg sublingual tablets was successfully finalised on 2010-06-03.

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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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