LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Metadon Pharmadone
(methadone hydrochloride)

SE/H/1311/01-20/MR

This module reflects the scientific discussion for the approval of Metadon Pharmadone. The procedure was finalised at 2013-02-13. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Pharmadone AB has applied for a marketing authorisation for Metadon Pharmadone, oral solution, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150 mg. The active substance is methadone hydrochloride. For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Metadon Pharmadone is presented in the form of an oral solution containing 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 70, 80, 90, 100, 110, 120, 130, 140, or 150 mg of methadone hydrochloride. The excipients are raspberry flavour, glucose monohydrate, methyl parahydroxybenzoate, sucrose and water. The oral solutions are filled in plastic bottles.

II.2 Drug Substance

Methadone hydrochloride has a monograph in the Ph Eur.

Methadone hydrochloride is a white or almost white, crystalline powder which is soluble in water and freely soluble in ethanol. The structure of methadone hydrochloride has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on chirality is presented. 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

Metadon Pharmadone, oral solution is formulated using excipients described in the current Ph Eur, except for raspberry flavour, which is controlled according to acceptable in house specifications. 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 Introduction

IV.2 Pharmacokinetics

This is a well established use complete application of an oral methadone solution. The pharmacokinetics of methadone based on information in the literature has been provided. The oral bioavailability is high but variable (41-95%). Methadone is a p-gp substrate. The binding to plasma proteins varies between 60-90 %. The plasma elimination half-life is approximately 15-60 hours (for the racemate). The main metabolism takes place in the liver where a number of inactive metabolites are formed (2-ethyliden-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) and a secondary metabolite to EDDP, 2-ethyl-5-methyl-3,3-diphenyl-1-pyrrolidine (EMDP). Two other active metabolites are formed but are present in smaller amounts, approximately 2 % (metadol and nor-metadol). Several other metabolites are formed and between 20-40 % of the administered dose has not been identified. There is a significant difference in the pharmacokinetics between the two enantiomers. The active S-enantiomer has a fu of approximately 10 % (the less active, approximately 1/10 the S-enantiomer, has a fu of 14 %). The main metabolising enzyme is CYP3A4, but also CYP2D6, 2C9, 2C19, 2B6 and 1A2 may contribute. Methadone is therefore mainly sensitive to CYP3A4 inhibition and induction. Methadone may also have some autoinduction properties. The excretion via the kidney is urine pH sensitive. The overall literature review provided on the pharmacokinetics of methadone is considered sufficient.

IV.3 Pharmacodynamics

Opioid-induced euphoria occurs only at high plasma (and brain) levels and is therefore mostly related to i.v. abuse. Oral methadone administration does not cause euphoria when tolerance is well developed and the dose is right. In a well stabilized Methadone Maintenance patient the straight period is 24-32 hours. This silent, symptom-free stage is peculiar for opioid dependence and does not occur for instance with sedative or central stimulant dependence, although they all have tolerance development and cross-tolerance within their respective dependency groups.

IV.4 Clinical efficacy

The clinical efficacy of Methadone Maintenance Treatment (MMT) has been repeatedly proven beyond any doubt, including 3 trials against drug-free treatment and comparisons of mortality rates between untreated heroin addicts and methadone maintenance treated patients (Grönbladh et al. 1990, not mentioned here). Since methadone is a heavy opioid narcotic, this treatment must be reserved for subjects who have entered the compulsive stage of dependency. As a rule this takes 2 years of intensive heroin abuse, and patients should only be admitted following serious attempts in drug-free treatment programmes (Frykholm & Gunne 1980, not mentioned here). According to Swedish National guidelines buprenorphine maintenance should be tried first, if the degree of dependency is low or unknown. A transfer to MMT is actualized only if the highest recommended buprenorphine dose is not adequate.

IV.5 Clinical safety

The application mentions the following side-effects: constipation, weight gain, reduced libido, and irregular menstruations. These side-effects have been reported, but it might be mentioned that female heroin addicts have generally suffered from amenorrhoea during their years of heroin abuse. What is not mentioned is the QT-prolonging effect of high methadone doses, which have been reported since 2003 and are becoming an increasing problem due to the tendency in some programs to use higher methadone doses than before. QT prolongation, cardiac irregularities, Torsades de Pointes and deaths from cardiac arrest occur dose dependently at methadone doses above 150 mg/day. Therefore the 160 mg strength was recommended to be withdrawn; which the company has followed. The MPA will soon issue treatment guidelines to prevent unnecessary deaths from this treatment.

IV.6 Discussion on the clinical aspects

Methadone Hydrochloride is a well established substance with known safety profile. Methadone has been used in treatment of opiate dependence for over 40 years, and during that period the use of Oral Solutions has also become well established. The submitted publications support this. The 20 products included in this application are oral solutions. One dose (50 ml) oral solution contains doses for single use between 10-150 mg.

Similar products of various strengths already exist on the EU market. The applicant has provided evidence for the efficacy and safety of this product.

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 Metadon Pharmadone, oral solution, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150 mg is recommended for approval.

VI. APPROVAL

The Mutual recognition for Metadon Pharmadone, oral solution, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150 mg was successfully finalised on 2013-02-13.

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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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