LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Metadon Nordic Drugs
(methadone hydrochloride)

SE/H/1352/01-25/MR

This module reflects the scientific discussion for the approval of Metadon Nordic Drugs. The procedure was finalised at Day 22. 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.mpa.se E-mail: registrator@mpa.se

I. INTRODUCTION

The application for Metadon Nordic Drugs, oral solution, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, is a well-established use application made according to Article 10a of Directive 2001/83/EC. The applicant, Nordic Drugs AB, applies through the Mutual Recognition Procedure with Sweden acting as reference member state (RMS) and NO and FI as concerned member states (CMS).

For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Metadon Nordic Drugs is presented in the form of oral solution containing the drug substance methadone hydrochloride. The excipients are sucrose, glucose monohydrate, methyl parahydroxybenzoate (E 218), raspberry aroma and water.

The solution is packed in a plastic bottle with a child-resistant cap.

II.2 Drug Substance

Methadone hydrochloride has a monograph in the Ph Eur.

The structure of methadone 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/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 Nordic Drugs oral solution is formulated using excipients described in the current Ph Eur, except for raspberry aroma which is controlled according to acceptable in house specifications. All raw materials used in the product are of vegetable origin or have 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 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.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of methadone are well known. As methadone is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate. The non-clinical overview has been written by Dr Michael Kroll and dated 28th of October 2008. Report refers 85 publications up to year 2008. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

III.1 Ecotoxicity/environmental risk assessment

The use of Metadon Nordic Drugs is not considered to increase the risk to the environment beyond or above that which may be caused by other pharmaceuticals containing methadone.

IV. CLINICAL ASPECTS

IV.1 Introduction

Methadone is an opioid analgesic and is used clinically in pain therapy as well as for substitution therapy in opioid addiction. Methadone is well recognised in the management of moderate to severe pain related either to cancer or to other pathological conditions as well as in the treatment of opioid dependence including opioid detoxification and maintenance therapy.

IV.2 Pharmacokinetics

This is a well established use complete application of an oral methadone solution. No specific pharmacokinetic studies are required for this formulation, because no differences to other approved methadone oral solutions are expected at time of administration since the active substance is dissolved. The application included a clinical summary, based on literature reviews, where the pharmacokinetics of methadone was adequately presented.

IV.3 Pharmacodynamics

Methadone is a synthetic potent competitive opioid agonist, which like morphine and heroin acts mainly on the μ-receptors, which are assumed to be particularly important for analgesia, euphoria, respiratory depression, tolerance and dependence. Since methadone is a competitive agonist with a strong affinity towards μ-receptors, methadone at adequate therapeutic doses in maintenance therapy will reduce the effect of other opioids like heroin. Methadone also has N-

methyl-D-aspartate (NMDA) receptor activity. By antagonising the NMDA receptor, methadone may decrease craving for opioids and tolerance, and this may be a possible mechanism for its efficacy in the treatment of neuropathic pain.

IV.4 Clinical efficacy

The clinical efficacy of methadone maintenance treatment in opioid addiction has been repeatedly proven beyond any doubt, including a number of comparative trials against drug-free treatment and comparisons of mortality rates between untreated heroin addicts and methadone maintenance treated patients. The Clinical overview includes a review of literature with efficacy comparisons between methadone and no pharmacological treatment, and between methadone and buprenorphine. Efficacy at long-term use and efficacy in special populations has also been reviewed.

IV.5 Clinical safety

The Clinical overview includes an adverse reaction table based on a previously approved methadone oral solution, and a literature review. In addition, a comparison of adverse events in studies comparing methadone and adrenergic agonists in heroin/opiate addicts is included.
A discussion on the risk for QT-prolongation with methadone is included in the submitted documentation. Cases of prolonged QT interval and torsade de pointes have been reported during treatment with methadone, especially in high doses (> 100 mg/day). Due to the risk for QT-prolongation and torsade de pointes, methadone should be administered with care to patients potentially at risk of developing QT prolongation, e.g. patients with previous arrhythmias, severe cardiac disease or ischemic heart disease, a family history of sudden death at young age, electrolyte anomalies (hypokalaemia, hypomagnesaemia), and concomitant treatment with CYP 3A4 inhibitors or medicinal drugs known to cause electrolyte anomalies. The highest recommended dose, which should be used only rarely, is 150 mg/day. For patients who are treated concomitantly with CYP3A4 inducers, higher doses may be needed.
Appropriate warning texts regarding the risk for QT prolongation are included in the SmPC.

IV.6 Discussion on the clinical aspects

Methadone is an opioid analgesic and is used clinically in pain therapy as well as for substitution therapy in opioid addiction. Methadone may in highly opioid-tolerant individuals at certain dose levels offer a 24 – 30 h blockade of craving, without a concomitant state of euphoria. The main medical risk involved in maintenance treatment with methadone is due to QT-prolongation at the higher end of the recommended dose range, which is sometimes combined with torsade de pointes and even cardiac arrest. A limitation in the highest recommended dose is therefore stated as 150 mg. In some cases, e.g. in those patients on CYP3A4 inducers, higher doses may be needed. These doses should only be administered with care. A specific wording on this has been included in the product information.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The risk/benefit ratio is considered positive and Metadon Nordic Drugs, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, oral solution, is recommended for approval.

User consultation

The user test was assessed and accepted with the first national approval 111:2009:47615-17639. A bridging to Martindale Pharmas user test was accepted by the MPA, as the leaflets were identical. A full user test regarding the layout was performed by GfK Healtcare and found acceptable by the MPA.

VI. APPROVAL

The Mutual recognition procedure for Metadon Nordic Drugs, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, oral solution, was successfully finalised on 2014-07-23.

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

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)

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.mpa.se E-mail: registrator@mpa.se