LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Metadon 2care4
(methadone hydrochloride)

SE/H/1713/01-04/DC

This module reflects the scientific discussion for the approval of Metadon 2care4. The procedure was finalised on 2018-07-18. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

2care4 Generics ApS has applied for a marketing authorisation for Metadon 2care4, 5 mg, 10 mg, 20 mg and 40 mg, tablet. The active substance is methadone hydrochloride. Methadone is a narcotic analgesic which belongs to the same group as morphine. The substance has an agonist effect on the opioid receptors in the brain, bone marrow and the nervous system, with high affinity for μ-receptors as well as some affinity for σ- and κ-receptors. Methadone acts in a similar way as morphine, but has a less sedative effect.

For approved indications, see the Summary of Product Characteristics.

The marketing authorisation has been granted pursuant to Article 10a 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 methadone has been provided, which was based on scientific literature. Methadone is a widely used, well-known active substance and 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.

III.1 Ecotoxicity/environmental risk assessment

Approval of Metadon 2care4 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 Discussion on the non-clinical aspects

There are no objections to approval of Metadon 2care4 from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Methadone is a well-known substance, and the summary of clinical pharmacology provided as well as the recommendations in the SmPC regarding e g special populations and interaction risks, are in general in line with SmPCs of similar products already approved in Sweden.

To justify that the submitted efficacy and safety data in the published studies submitted are applicable to the new formulation Metadon2care4, the Applicant has not performed any bioequivalence study, but submitted a biowaiver justification. References have been submitted to support high solubility and permeability, and it is accepted that methadone is a BCS class I substance. The formulation has a very rapid dissolution and the excipients are well-known and are not known to impact the in vivo performance of drugs. Methadone has previously not been considered to be a narrow therapeutic index drug. Taken together, all guideline requirements regarding a BCS-based biowaiver are met for Metadon 2care4, and no relative bioequivalence study is needed to show that the literature data provided is applicable for the new formulation.

IV.2 Pharmacodynamics

The applicant has provided a summary of the pharmacodynamics of methadone hydrochloride, which is considered acceptable.

IV.3 Clinical efficacy

The applicant has provided an overview on clinical studies performed in the treatment of cancer pain, non-cancer related pain, opioid detoxification, methadone maintenance treatment for opioid dependent patients and management of opioid dependence in special populations. This overview is considered acceptable.

IV.4 Clinical safety

The applicant has provided an overview of clinical safety, which is considered acceptable.

It was concluded that the product should not be contra indicated in children. However, due to a higher sensitive to adverse drug reactions in children, intoxications, a long half-life and difficulties in dosing, methadone is not recommended in children.

IV.5 Risk Management Plans

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 Metadon 2care4.

Safety specification

Summary of safety concerns	
Important identified risks	- QT-interval prolongation (including Torsade de Pointes); - Use in patients with hepatic or renal impairment; - Intoxication in children; - Interaction in MAO inhibitors; - Interaction with CYP3A4 inducers or inhibitors; - Respiratory depression.
Important potential risks	- Use during pregnancy and breastfeeding.
Missing information	- Use in children.

Only routine pharmacovigilance activities and risk minimization measures are proposed.

Publications in the Clinical overview provided by the Applicant, as well as some additional limited publications and dosing formula provided by assessors, give some support to a beneficial effect of methadone in the treatment of severe pain of different origin in children without major adverse events. Consequently, use in children may not be considered as missing information. The Applicant was asked to consider deleting the missing information “use in children” from the list of safety concern at the next regulatory RMP update.

Only routine pharmacovigilance activities and risk minimization measures are proposed.

Pharmacovigilance Plan

Routine pharmacovigilance activities conducted for all the medicinal products include:

- collection, processing, management, quality control, follow-up for missing information, coding, classification, duplicate detection, evaluation and timely electronic transmission of individual case safety reports (ICSRs) from any source;
- signal management;
- scheduling, preparation (including data evaluation and quality control), submission and assessment of periodic safety update reports.

Risk minimisation measures
The summary of safety concerns is adequate and only routine pharmacovigilance activities and risk minimization measures are proposed.

Summary of the RMP
The submitted Risk Management Plan, Version 1, signed 27 June 2017 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. The Applicant was asked to consider deleting the missing information "use in children" from the list of safety concern at the next regulatory RMP update.

An updated RMP should be submitted:

- At the request of the RMS;
- 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 Metadon Abcur SE/H/1288/01-02/MR (content) and Folic Acid GSP 16/H/0121/001 (layout). The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

This application is based upon Article 10a of Directive 2001/83/EC, as amended. The Applicant is claiming that the constituent of the medicinal product i.e. Methadone Hydrochloride Tablets has a well-established use, with an acceptable level of safety and efficacy, as outlined in Part II.1 of Annex I to Directive 2001/83/EC. Quality as well as clinical efficacy and safety is considered acceptable. The application is 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

The Decentralised procedure for Metadon 2care4, 5 mg, 10 mg, 20 mg and 40 mg, tablet was positively finalised on 2018-07-18.

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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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