LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Metadon Abcur
(methadone hydrochloride)

SE/H/1682/01-04/DC

This module reflects the scientific discussion for the approval of Metadon Abcur. The procedure was finalised on 2017-12-12. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Abcur AB has applied for a marketing authorisation for Metadon Abcur, 5 mg, 10 mg, 20 mg and 40 mg, tablet. The active substance is methadone hydrochloride.

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 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

III.1 Introduction

The non-clinical part of the application was submitted as a bibliography. No new non-clinical data have been supplied with this application and none are required for an application of this type. A non-clinical expert report has been written by a suitably qualified person and is satisfactory.

III.2 Pharmacology

Methadone (6-dimethylamino-4,4-diphenyl-3-heptanone) is a synthetic μ-opioid receptor agonist; in addition to its opioid receptor activity, it is also an antagonist of the N-methyl-D-aspartate (NMDA) receptor. Methadone is a racemic mixture of 2 enantiomers; the l- (R-; -) form is more potent, with a 10-fold higher affinity for opioid receptors, while d- (S-; +) methadone is the NMDA antagonist.

The non-clinical pharmacology of methadone has been has been thoroughly investigated. In vitro and in vivo studies provide support for the μ-opioid receptor agonistic and the N-methyl-D-aspartate receptor antagonistic action of methadone. Non-clinical evaluations of the potential of methadone as a substitute in opioid dependence and its analgesic activity is revealed by in vivo studies performed in mice, rats, dogs and monkeys, according to models recognized as being predictive and also applied during the development of newer antidepressant agents (i.e. schedule of withdrawal associated reinforcement in opiate addiction, or tail-flick and paw-withdrawal).

III.3 Pharmacokinetics

The non-clinical absorption, distribution, metabolism and excretion of methadone is quite well characterised, mainly in rats and dogs.

III.4 Toxicology

The genotoxic potential of methadone was examined in vitro in bacteria, yeast and mammalian cell lines and in vivo in mice, rats and Drosophila melanogaster. Based on the presented data, it can be concluded that methadone has shown some genotoxic activity in in vitro assays, it appeared to cause numerical or structural chromosomal aberrations of the spermatocytes in mice, but no genotoxic effects were observed in vivo in rat bone marrow cells or in Drosophila melanogaster. None of the studies referred are GLP compliant and the study designs are not in agreement with recommendations in ICH S2B.Taken together, the data are inconsistent regarding to the genotoxic potential of methadone.

Two GLP-compliant long-term (2 years) carcinogenicity studies after oral administration in mice and rats, respectively, are described in the literature. It can be concluded that oral administration of methadone did not lead to a significant increase in tumor incidence in neither species.

Several reprotoxicology studies are available for methadone but most of them do not meet current standards. Collectively, the studies reflect what is already known regarding the risks involved with methadone treatment during pregnancy.

The published literature indicates that methadone can block ovulation, decrease male sexual drive and fertility. In mice, a teratogenic effect of methadone has been described, and additionally increased rate of preimplantation deaths, decreased fertility and detrimental effect on the developing nervous system. Foetal malformations are also described in other species such as marmots, hamsters and chickens. No malformations are reported in embryo-foetal development studies in rats and rabbits.

The effect of methadone on the pre- and postnatal development was also evaluated in several animal models and report that methadone exposure during gestation results in decreased pup weight (in mice, rats and monkeys). Some behavioural differences were also observed in rat pups born to methadone-treated dams including increased anxiety, altered open field activity, cage activity, passive avoidance latencies, shuttle box avoidances, and rotarod latencies. Moreover, rat infants exposed to methadone prenatally and postnatally via the dam's milk experienced opiate withdrawal syndromes, indicating that dependence can develop in the newborn during maternal drug exposure.

III.5 Ecotoxicity/environmental risk assessment

The MAH has provided a justification for the absence of an environmental risk assessment of methadone hydrochloride. The methadone products applied for are intended to replace the other identical products already on the market and the approval of these products should not result in an increase of the total quantity of methadone hydrochloride released into the environment.

III.6 Discussion on the non-clinical aspects

While the non-clinical testing of methadone is not up to the current standard, the well-established use of the product and the long clinical experience compensates for the non-clinical shortcomings.

IV. CLINICAL ASPECTS

IV.1 Introduction

Methadone is 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

The Applicant has submitted a thorough summary of published literature concerning the pharmacokinetics of methadone. In order to justify how efficacy and safety data presented in the bibliography may be extrapolated to Metadon Abcur, a biowaiver justification has been provided. The Applicant has satisfactorily justified that methadone is a BCS class I substance with high solubility and complete absorption.

Absorption
In several published in vivo studies, the mean absolute bioavailability of oral methadone was in the range of 85-86%. Results from in vitro studies indicate that methadone is a substrate for P-gp.

There is little information available regarding the possible influence on food intake on the absorption of methadone. No specific restriction needs to be included in the SmPC for this well-known active substance.

Distribution
The volume of distribution is approximately 5 L/kg. The plasma protein binding is up to 90%.

Elimination
Excretion
Approximately 20-60 % of the dose is eliminated in the urine in 96 hours (approx. 33 % in unmodified form, approx. 43 % as EDDP and approx. 5-10 % as EMDP). The quote between EDDP and unmodified methadone is usually much higher in the urine of patients in methadone treatment than at normal overdoses. Approximately 30 % of the dose is eliminated in faeces, but this part is normally decreased at higher doses. Approximately 75 % of the eliminated substance is in unconjugated form.

The terminal half-life of methadone has been reported to be in the range 20-52 hours after multiple-dose administration and 23 hours after a single-dose. In different studies mean clearance values of 81-134 ml/min have been reported.

Metabolism
Methadone undergoes hepatic N-demethylation and spontaneous intramolecular cyclization, which results in the formation of 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP), a pharmacologically inactive metabolite. EDDP can be a subject of further N-demethylation into 2-ethyl-5-methyl-3,3- diphenylpyraline (EDMP). The main enzymes responsible for the metabolism of methadone are CYP3A4 and possibly CYP2B6. However, there seems to be a lack of agreement as to their relative contribution to the overall metabolism. There is likely some contribution of CYP2C19 and CYP2D6 as well.

Special populations
Dose reduction or prolongation of the dosing interval is recommended in patients with severe hepatic and renal impairment. Dose adjustments based on age, gender, body weight do not appear necessary.

Interactions
Methadone is a substrate of CYP3A4, CYP2B6 and CYP2D6. Co-administration of inhibitors of these enzymes has resulted in decreased exposure of methadone. CYP3A4-inducers did conversely increase methadone exposure.

IV.3 Pharmacodynamics

Methadone is a synthetic diphenylheptane derivative, being primarily an opioid agonist with similar pharmacological effects to that of morphine. The effects of methadone are mediated via μ-opioid receptors, which are located within the central nervous system as well as throughout the peripheral tissues. The μ-opioid receptors are responsible for supraspinal analgesia, respiratory depression, euphoria, sedation, decreased gastrointestinal motility, and physical dependence.

IV.4 Clinical efficacy

Methadone is 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. With the multitude of opioid agonists available to the treating physician, the place of methadone in the indications claimed by the Applicant in current practice needs to be evaluated in light of current therapeutic guidelines, with recommendations ultimately summing up the extensive knowledge and evidence available.

Relevant studies on cancer related pain is discussed within the frames of this application. Recent therapeutic guidelines as well as reviews on the published trials on the efficacy of opioid analgesics have endorsed the evidence for methadone, as a potent and convenient analgesic.

The clinical efficacy of methadone maintenance treatment in opioid addiction has been repeatedly proven, including a number of comparative trials against drug free treatment and comparisons of mortality rates between untreated heroin addicts and methadone maintenance treated patients.

Detoxification by tapering dose of methadone is an alternative therapeutic approach for opioid withdrawal, however, primary emphasis of detoxification is not to achieve abstinence directly; it may rather be the first step towards alternative long-term treatments.

IV.5 Clinical safety

The safety profile of methadone, when used in the claimed indications, is well established. The most common adverse reactions to methadone are constipation, vomiting and dizziness; though serious adverse reactions such as QTc prolongation or torsades de pointes are also known. The pharmacological basis for most of the adverse reactions to methadone resides in its agonist binding to the μ-receptors being responsible for the respiratory depression, euphoria, sedation, decreased gastrointestinal motility and dependence.

Methadone has an established risk profile associated to its use which arises mainly from the binding to μ-opioid receptors.

IV.6 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 Abcur.

RMP version 5, signed 7 December 2016 with data lock point of 28 November 2016, is acceptable.

The approved summary list of safety concerns with no additional pharmacovigilance or risk minimisation measures is as outlined below.

Summary of safety concerns	
Important identified risks	• Respiratory depression • QT interval prolongation (including Torsade de Pointes) at doses >100 mg/day • Use in patients with hepatic impairment • Use in patients with renal impairment • Abuse/Misuse/dependence • Use in patients with intestinal pseudo-obstruction, acute abdomen and inflammatory bowel disease • Intoxication in children • Interactions with MAO inhibitors • Interaction with other CNS depressants • Drug interactions with CYP450 inducers and inhibitors • Overdose
Important potential risks	• Use in pregnancy and lactation • Medication error
Missing information	• None

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

The objective of routine risk minimisation measures for abuse/misuse/dependence is to minimise the risk of abuse/misuse/dependence associated with use of the drug product. The routine risk minimisation measures are to assess the frequency of reporting cases and the need to modify the risk/benefit profile for the product through routine pharmacovigilance activities. Other routine risk minimisation measures are controlled medical substance and prescription only medicine by registered physicians.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Identified Risks		
Respiratory depression	• Instruction on dosing in Section 4.2 of the SPC states that patients with decreased lung volume must receive a lower initial dose. • Contraindication in Section 4.3 of the SPC mentions that methadone is contraindicated in patients with respiratory depression and acute obstructive airway disease. • Warning in Section 4.4 of the SPC is to individually assess acute asthma attacks, severe obstructive pulmonary disease, cor pulmonale, impaired respiratory reserve, hypoxia and hypercapnia which are relative contraindications for methadone. • Interaction in Section 4.5 of the SPC mentions that medicinal products with a sedative effect on the central nervous system may give an increased respiratory depression. • Listed in Section 4.8 of the SPC, pulmonary oedema and respiratory depression are uncommon side effects reported with methadone. • Controlled medical substance and prescription only medicine by registered physicians.	None proposed
QT interval prolongation (including Torsade de Pointes) at doses >100 mg/day	• Instruction on dosing in the SPC Section 4.2 states that doses over 150 mg/day should as far as possible be avoided due to an increased risk of QT-prolongation, torsade de pointes and cases of cardiac arrest. • Warning in Section 4.4 of the SPC states that methadone should be administered with caution	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	to patients at risk to develop prolonged QT-interval and EKG should be monitored in all patients. • Interaction in Section 4.5 of the SPC mentions that methadone should not be combined with medicinal products which may prolong the QT-interval. • Listed in Section 4.8 of the SPC, bradycardia, palpitations, cases of prolonged QT-interval and torsades de pointes are rare side effects reported with methadone, especially at higher doses. • Controlled medical substance and prescription only medicine by registered physicians.	
Use in patients with hepatic impairment	• Instruction on dosing in the SPC Section 4.2 states that methadone should be administrated in a lower dose than the recommended and the clinical response of the patient with hepatic impairment should be used as guidance for further dosage. • Warning in Section 4.4 of the SPC states that methadone should be used with caution as metabolism of methadone may be reduced at impaired hepatic function. • Information in Section 5.2 of the SPC mentions that due to increased exposure, caution is advised in patient with hepatic impairment. • Controlled medical substance and prescription only medicine by registered physicians.	None proposed
Use in patients with renal impairment	• Instruction on dosing in the SPC Section 4.2 states that patients with urethral stricture or prostate hypertrophy must receive a lower initial dose. • Warning in Section 4.4 of the SPC states that methadone should be used with caution at impaired renal function. • Information in Section 5.2 of the SPC mentions that due to increased exposure, caution is advised in patients with renal impairment. • Controlled medical substance and prescription only medicine by registered physicians.	None proposed
Abuse/miuse/dependence	• None proposed • Controlled medical substance and prescription	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	only medicine by registered physicians. • MAH will assess the frequency of reporting cases and the need to modify the risk/benefit profile for the product through routine pharmacovigilance activities.	
Use in patients with intestinal pseudo-obstruction, acute abdomen and inflammatory bowel disease	• Warning in Section 4.4 of the SPC states that methadone should not be used in patients with intestinal pseudo-obstruction, acute abdomen and inflammatory bowel disease. • Interaction in Section 4.5 of the SPC mentions that concurrent use of methadone and antimotility products (loperamide and diphenoxylate) may result in severe constipation. • Listed in Section 4.8 of the SPC, constipation is a common side effect reported with methadone. • Controlled medical substance and prescription only medicine by registered physicians.	None proposed
Intoxication in children	• Instruction on dosing in the SPC Section 4.2 states that methadone must not be given to children. • Contraindication in Section 4.3 of the SPC mentions that methadone is contraindicated in children. • Warning in Section 4.4 of the SPC: Children are more sensitive than adults, which is the reason why poisoning may occur at very low doses. To avoid that children by mistake take methadone when it is used at home, it should be stored in a safe place, kept out of reach of children. • Section 6.5 of the SPC mentions that childproof HDPE-bottle with HDPE-cap is provided. • Controlled medical substance and prescription only medicine by registered physicians.	None proposed
Interactions with MAO inhibitors	• Contraindication in Section 4.3 of the SPC mentions thatconcurrent administration of MAO-inhibitors or administration within two weeks after terminated treatment with MAO-inhibitors is contraindicated. • Interaction in Section 4.5 of the SPC mentions that concurrent administration of MAO inhibitors may result in reinforced CNS-inhibition, severe hypotension and/or apnoea.	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	• Controlled medical substance and prescription only medicine by registered physicians.	
Interaction with other CNS depressants	• Warning in Section 4.4 of the SPC states that concurrent administration of other opiates, alcohol, barbiturates, benzodiazepines and other strong sedative pshycoactive drugs may potentiate the effect and the undesirable effects of methadone and should be avoided. • Interaction in Section 4.5 of the SPC mentions that medicinal products with a sedative effect on the central nervous system may give an increased respiratory depression, hypotension, strong sedation or coma. • Controlled medical substance and prescription only medicine by registered physicians.	None proposed
Drug interactions with CYP450 inducers and inhibitors	• Interaction in Section 4.5 of the SPC mentions that caution should be taken during concomitant use of methadone with CYP3A4-inducers and inhibitors. • Controlled medical substance and prescription only medicine by registered physicians.	None proposed
Overdose	• Instruction on dosing in the SPC Section 4.2 states that extreme caution is necessary when methadone is administered more frequently during initiation of methadone treatment in order to maintain adequate analgesic effect. • Section 4.9 of the SPC describes the symptoms and treatment of severe overdosage of methadone. • Controlled medical substance and prescription only medicine by registered physicians.	None proposed
Important potential risks		
Use in pregnancy and lactation	• Information in the SPC Section 4.6 describes that use of methadone immediately before and after delivery is not recommended due to the risk of neonatal respiratory depression. Also methadone is excreted in breast milk, so breast feeding may be performed at doses up to 20 mg daily. At higher doses the benefits of breast feeding must be weighed towards the possible negative effects of the child. . • Information in the SPC Section 5.3 mentions that methadone at high doses caused	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	malformations in marmots, hamsters and mice, in which most of the reports dealing with exencephaly and defects in the central nervous system. • Controlled medical substance and prescription only medicine by registered physicians.	
Medication error	• Section 3 of the SPC describes the pharmaceutical form of different strengths of methadone tablets. • Instructions on dosing in SPC Section 4.2 explains the dose in opioid naive patient and dose in non opioid naive patient. It also explains the maintenance treatment for opioid dependence. • Controlled medical substance and prescription only medicine by registered physicians.	None proposed
Missing information		
None		

Summary of the RMP

The RMP is approved

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.

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

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 Danish.
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.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Methadone has been in clinical use in the same formulation/administration route and indication and dosing strategies as for the applicants' product in EU for decades. The applicant has presented a summary of publications of efficacy and safety.

However, only a few of the clinical studies are of appropriate design and they are based on relatively few patients. This lack of published clinical studies of appropriate design is compensated for by the fact that methadone has been used clinically in pain therapy as well as for substitution therapy in opioid addiction for decades and products having the same pharmaceutical form and indications as those of the Applicant's Methadone hydrochloride tablets have been available on the European market since decades.

No new or unexpected safety concerns arose from the application, but the main medical risk involved in maintenance treatment with methadone is due to QT-prolongation at the higher end of the recommended dose ranges, which is sometimes combined with torsade de pointes and even cardiac arrest. A risk management plan has been developed to ensure that Metadon Abcur is used as safely and safety information has been included in the product information for Metadon Abcur, including the appropriate precautions to be followed by healthcare professionals and patients.

The benefit/risk ratio is considered positive and Metadon Abcur, 5 mg, 10 mg, 20 mg and 40 mg, tablet is recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83 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 Abcur, 5 mg, 10 mg, 20 mg and 40 mg, tablet was positively finalised on 2017-12-12.

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MEDICAL PRODUCTS AGENCY

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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