IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Methadone hydrochloride 1 mg/ml oral solution
Methadone hydrochloride
PA2128/002/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Methadone hydrochloride 1 mg/ml oral solution, from Alkaloid INT d.o.o. on June 2019 for "*Substitution therapy for maintenance of opioid dependence in adults in conjunction with appropriate medical, social and psychosocial care*".

The application was submitted as a well-established application, as per Article 10a of Directive 2001/83/EC.

With IE as the Reference Member State in this Decentralised Procedure, Alkaloid applied for the Marketing Authorisations for Methadone hydrochloride 1 mg/ml oral solution in HR, MT, PL, UK. [Concerned Member States(CMSs)]

This product will be subject to prescription.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website.

Name of the product	Methadone hydrochloride 1mg/1ml Oral Solution
Name(s) of the active substance(s) (INN)	Methadone hydrochloride
Pharmacotherapeutic classification (ATC code)	N07BC02
Pharmaceutical form and strength(s)	1mg/1ml Oral Solution
Marketing Authorisation Number(s) in Ireland (PA)	PA2128/002/001
Marketing Authorisation Holder	Alkaloid - INT d.o.o
MRP/DCP No.	IE/H/549/001/DC
Reference Member State	IE
Concerned Member State	HR MT PL UK (Nothern Ireland)

II. QUALITY ASPECTS

II.1. Introduction

This application is for Methadone Hydrochloride 1 mg/ml oral solution

II.2 Drug substance

The active substance is methadone hydrochloride, an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP).

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

The product contains 1 mg/ml of methadone hydrochloride.

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

All ingredients comply with the Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for the dosage form, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Methadone Hydrochloride 1 mg/ml oral solution.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of methadone hydrochloride are well known. As methadone hydrochloride is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate. A brief summary of the extensive literature submitted is provided below:

III.2 Pharmacology

The pharmacological activity of methadone is mediated primarily via the μ-opioid receptor. It is an enantiomeric drug administered as a racemate. The analgesic activity is primarily related to the activity of the l-enantiomer whereas the d-enantiomer has more activity as an NMDA receptor antagonist which may be related to its ability to prevent opioid withdrawal symptoms. Studies in morphine dependent rats and mice adequately demonstrate the effectiveness of methadone in alleviating opiate withdrawal symptoms. Literature on non-GLP studies pertaining to safety pharmacology endpoints adequately discuss the known class related effects of opiates on respiratory, GI and CNS function.

III.3 Pharmacokinetics

The literature submitted by the applicant sufficiently summarises the ADME of methadone in non-clinical species. Furthermore, information on potential PK DDI with a number of other actives are presented. Relevant information is included in the SmPC.

III.4 Toxicology

The primary toxicological risk associated with opiate treatment is dose dependent suppression of respiratory function. The applicant has submitted literature covering studies which characterise the effects repeated methadone administration to rats, mice, NHP and guinea pigs for durations of up to two years. Genotoxicity studies summarised were not conducted to GLP, but do appear to be of good quality. Methadone did not induce mutations in salmonella in a bacterial Ame's test in either the presence or absence of metabolic activation, it was weakly positive for induction of mutations in E-coli strain WP2uvrA. This effect was very marginal and did not appear to be dose dependent, this positive finding is hence questionable. Methadone did not induce chromosomal aberrations in rat bone marrow cells following in-vivo administration. The submitted literature on genotoxicity is considered adequate. Hence, it can be concluded that although methadone did show some evidence of mutagenicity in in-vitro assays, the relevance to human risk assessment is unclear. Methadone administration was associated with significant reproductive toxicity. Reproductive toxicological studies summarised were non-standard in nature and not conducted to GLP. Adverse effects reported included direct effects on male fertility evidenced through altered foetal viability and development following mating of methadone exposed males to naïve females. Methadone was not teratogenic in rats or rabbits but there was evidence of an increase in the incidence of (CNS) malformations in mice and hamsters. Prenatal exposure to methadone in rat produces a number of adverse effects on offspring with the CNS as the primary target organ for toxicity. Methadone was present in the milk of rats at levels high enough to induce dependence in offspring.

III.5 Ecotoxicity/environmental risk assessment

The applicant's justification that as methadone HCL solution is intended for generic substitution it is unlikely to significantly add to the environmental risk posed by methadone already is reasonable. To support this assertion, the applicant has provided 3-year consumption data from 4 European countries which do not indicate a significant increase in consumption in that time period. It is accepted that Methadone hydrochloride 1 mg/ml oral solution is unlikely to significantly increase the environmental burden of methadone HCL and therefore no further assessment of environmental risk is warranted.

III.6 Discussion on the non-clinical aspects

As methadone is a well-known active substance, this is a bibliographic application with no new non-clinical studies conducted by the applicant. The submitted overview of the available non-clinical pharmacodynamic, pharmacokinetic and toxicological data is acceptable.

IV. CLINICAL ASPECTS

IV.1 Introduction

This applicantion was submitted as a well-established application, as per Article 10a of Directive 2001/83/EC, a bibliographic application based on a systematic review of the literature. The active substance of the product Methadone hydrochloride 1 mg/ml oral solution is methadone hydrochloride.

The active substance is not considered a new active substance.

No new clinical study has been conducted by the applicant. The applicant claims that Methadone has a well-established use with an acceptable level of safety and efficacy, as outlined in Part II.1 of Annex I of Directive 2001/83/EC. The Clinical Overview is based entirely on published scientific literature.

Methadone in the pharmaceutical form of the medicinal product Methadone hydrochloride is presented in a liquid oral dosage form and concentration (1mg/ml) which are well-established in the Community and have been extensively used for the proposed therapeutic indication for more than 10 years.

This pharmaceutical form is used for the treatment of opioid dependence in the EU for decades. The currently proposed indication is already accepted for many other marketed liquid oral methadone-containing products.

The active substance methadone fulfils the criteria necessary to justify the legal basis of the application.

The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

Indication:
Methadone hydrochloride 1mg/1ml Oral Solution is indicated for the

"*Substitution therapy for maintenance of opioid dependence in adults in conjunction with appropriate medical, social and psychosocial care*".

For full details on posology and full prescribing information please see the SmPC for Methadone hydrochloride 1mg/1ml Oral Solution.

Posology
Dosage should be titrated to individual needs of patients. Local clinical guidance may differ from the posology described hereafter and should be followed.
Substitution treatment with methadone should be prescribed by a doctor with experience in treating opiate/opioid-dependent patients, preferably at centres that have specialised in the treatment of opiate/opioid dependency.
The dose is based on the occurrence of withdrawal symptoms and must be adjusted for each patient according to his or her individual situation and the way he or she feels. In general, after adjustment of the dose, the aim is to administer the lowest possible maintenance dose.

Adults
In general the initial dose will be between 10-30 mg. The first dose given to a patient who has not recently used opioids should be no greater than 10-20 mg. In cases where tolerance to opioids is high, the normal initial dose will be between 25-40 mg. The patient should be observed 3-4 hours after the first dose has been taken. If the patient is showing signs of overdose, continue to monitor the patient at fifteen- minute intervals. If the patient enters a coma, administer naloxone as a prolonged infusion.
In reaching the maintenance treatment it is recommended that the dose is increased by maximum 10 mg at a time. Dose increases should not be greater than 20 mg per week. The majority of individuals in maintenance treatment will require 60-120 mg per day for an effective and safe treatment, some may however need a higher dosage. The dosage should be determined based upon the clinical evaluation.
Physicians need to be aware of and adhere to currently accepted guidelines regulations and recommendations for treating opioid dependent patients including integrating psychosocial treatments and behaviour modification strategies for optimal results.
Dosing and duration should be individualised based on a careful evaluation of subjective and objective patient data, bearing in mind clinical status, including hepatic or renal function of the patient.

IV.2 Pharmacokinetics

No new pharmacokinetic data specific for this product has been submitted. The literature submitted by the applicant sufficiently summarises the known pharmacokinetics of methadone.
Methadone is one of the more lipid-soluble opioids and is well absorbed from the gastrointestinal tract, but undergoes fairly extensive first-pass metabolism. The bioavailability is above 80%. Steady state concentrations are reached within 5-7 days. Methadone is bound to albumin and other plasma proteins and to tissue proteins (probably lipoproteins), the concentrations in the lung, liver and kidneys being much higher than in blood. The metabolism of methadone is catalysed primarily by CYP3A4, but CYP2D6 and CYP2B6 are also involved, to a smaller extent. Methadone has a long elimination half-life (usually 20–37 hours), which allows for a once-daily dosing schedule.

IV.3 Pharmacodynamics

The literature submitted by the applicant sufficiently summarises the known pharmacodynamics of methadone.
Methadone is a strong opioid agonist with actions predominantly at the μ receptor. The analgesic activity of the methadone racemate is almost entirely due to the l-isomer, which is at least 10 times more potent as an analgesic than the d-isomer. The d-isomer lacks significant respiratory depressant activity but does have anti-tussive effects. Methadone also has some agonist actions at the κ and δ opiate receptors. These actions result in analgesia, depression of respiration, suppression of cough, nausea and vomiting (via an effect of the chemoreceptor trigger zone) and constipation.

An effect on the nucleus of the oculomotor nerve, and perhaps on opioid receptors in the pupillary muscles, causes pupillary constriction. All these effects are reversible by naloxone. Like many basic substances, methadone enters mast cells and releases histamine by a non-immunological mechanism. It causes a dependence syndrome of the morphine type.

IV.4 Clinical Efficacy

The evaluation of the clinical efficacy of methadone has been performed on a bibliographic basis. The methodological basis for the preparation of the efficacy segment is acceptable.
The efficacy of methadone is well known. The first research demonstrating the effectiveness of methadone for the treatment of opioid dependence was published over 40 years ago.
The indication for Alkaloid's methadone hydrochloride 1 mg/ml oral solution is: "*Substitution therapy for maintenance of opioid dependence in adults in conjunction with appropriate medical, social and psychosocial care*".
Treatment of illicit drug dependence typically involves a combination of pharmacotherapy and psychosocial interventions.
Four Cochrane reviews (Mattick 2009, Mattick 2014, Gowing 2011 and Faggiano 2003) were taken into consideration in support of methadone efficacy. Faggiano 2003 was used when considering methadone dose recommendation.

IV.5 Clinical Safety

Based on the clinical studies provided by the applicant, the safety of methadone is considered as well-established.

A large body of scientific evidence suggests that methadone treatment, when delivered to an appropriate standard of care, is a safe substitution medication for opioid dependence

Methadone maintenance treatment (MMT) has a long history of effectiveness and safety as a
therapy for opioid addiction. However, since it is a highly potent drug, methadone's improper prescription and/or its misuse can be harmful or even fatal.
Although methadone has been shown to have a favorable safety profile when used as indicated and few serious adverse reactions and no cumulative organ damage have been associated with daily administration of appropriate doses over more than 30 years in some patients, there are also risks associated with its use. Methadone is a very potent drug which, if it accumulates in the body, can cause respiratory depression and hypoxia, sometimes accompanied by pulmonary edema and/or aspiration pneumonia.

While the Cochrane reviews mentioned are limited in their treatment of adverse effects, as would be expected from reviews of RCTs in the main, they do provide some evidence of the
safety of methadone. None of the more serious adverse effects that could be predicted from an opioid agonist (such as respiratory depression, hepatic necrosis and hepatitis, hallucinations, bronchospasm, angioneurotic oedema or anaphylactic shock) were noted in any of the studies included in these reviews.

<u>Overdose and deaths related to methadone</u>
Overdosage of may result in respiratory depression (characterised by a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration and cyanosis), extreme somnolence (eventually progressing to stupor or coma), maximally constricted pupils, skeletal-muscle flaccidity, cold and clammy skin, and, sometimes, bradycardia and hypotension. In severe overdosage, particularly by the intravenous route, this may result in apnoea, circulatory collapse, cardiac arrest, and death.

<u>Contraindications</u>
Methadone should not be used in cases of:
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1;
- Use during an acute asthma attack;
- Respiratory depression, especially in the presence of cyanosis and excessive bronchial secretions;
- Acute alcoholism;
- Head injury and raised intracranial pressure;
- Concurrent administration with monoamine oxidase (MAO) inhibitors or within 2 weeks of discontinuation of treatment with them;
- Absence of dependence on opioid substances;
- Individuals with QT prolongation, including congenital long QT syndrome;
- As with all opioid analgesics, this product should not be administered to patients with severe hepatic impairment as it may precipitate porto-systemic encephalopathy in patients with severe liver damage.
- Ulcerative colitis, since it may precipitate toxic dilatation or spasm of the colon;

Biliary and renal tract spasm.
Use during labour is not recommended; the prolonged duration of action increases the risk of neonatal respiratory depression.

Please see the SmPC for Methadone hydrochloride 1 mg/ml oral solution for full details on the warnings and precautions relating to Methadone these include: Dependence/tolerance/withdrawal/ Respiratory depression
Details on Interactions with other medicinal products can also be found in the SmPC.

Undesirable effects
The adverse effects of methadone are generally the same as with other opioids, most commonly nausea and vomiting, that is observed in approximately 20% of the patients that go through methadone outpatient treatment.
Long term use of methadone may lead to morphine-like dependence. The abstinence syndromes are similar to the ones observed with morphine and heroine, however less intense, but more long-lasting.
The most serious adverse effect of methadone is respiratory depression, which may emerge during the stabilisation phase. Apnoea, shock and cardiac arrest have occurred.

Please see the SmPC for Methadone hydrochloride 1 mg/ml oral solution for the full list of adverse effects.

Risk Management Plan
The applicant 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 Methadone Alkaloid 1mg/1ml oral solution. The revised RMP (version 0.3 dated final sign off 10/03/2019) is acceptable. Routine risk minimization activities are considered sufficient. The applicant is requested to ensure it maintains the RMP in line with the latest SmPC updates and maintains regular reviews.

Summary table of safety concerns as approved in RMP

Important identified risks	Cardiac disease; Respiratory depression; Use in patients with hepatic impairment; Use in patients with renal impairment; Drug interaction;
Important potential risks	Use in pregnancy and lactation;
Missing information	None

Periodic Safety Update Report (PSUR)
With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c (7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- For medicinal products that do not fall within the categories waived of the obligation to submit routine PSURs by the revised pharmacovigilance legislation, the MAH should follow the DLP according to the EURD list.

IV.6 Discussion on the clinical aspects

The applicant submitted a well-established application, as per Article 10a of Directive 2001/83/EC, a bibliographic application based on a systematic review of the literature.
Methadone in the pharmaceutical form of the medicinal product Methadone hydrochloride is presented in a liquid oral dosage form and concentration (1mg/ml) which are well-established in the Community and have been extensively used for the proposed therapeutic indication for more than 10 years. The benefits of substitution treatment with methadone are well-documented.

Oral methadone has demonstrated a favourable safety profile when properly prescribed and used over the decades.

V. OVERALL CONCLUSIONS

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted, considered that Methadone hydrochloride 1 mg/ml oral solution, demonstrated adequate evidence of efficacy for the approved indication as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

Common renewal date will be 5 years after the finalisation of the procedure.