COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Methadon HCl Expharma 5 mg, 10 mg and 20 mg tablets

(methadone hydrochloride)

NL Licence RVG 119925-119927

Date: 9 December 2022

This module reflects the scientific discussion for the approval of Methadon HCl Expharma 5 mg, 10 mg and 20 mg tablets. The marketing authorisation was granted on 20 February 2018. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MMT	Methadone Maintenance Therapy
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Methadon HCl Expharma 5 mg, 10 mg and 20 mg tablets from ExtractumPharma Ltd.

The product is indicated for:

- Short-term treatment of moderate, severe and very severe pain when no causal treatment is possible.
- Treatment of heroin/opioid withdrawal symptoms during detoxification.
- Maintenance treatment in opioid addicted individuals without a direct abstinence perspective.

A comprehensive description of the indications and posology is given in the SmPC.

This national procedure concerns a bibliographic application based on the well-established medicinal use of methadone. No new (pre)clinical studies were conducted. The MAH submitted non-clinical and clinical overviews based on scientific literature.

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Methadon HCl Expharma 5 mg is a white or almost white, round, flat, uncoated tablet scored on one side and imprinted “M5” on the other side. Each tablet contains 5 mg of methadone hydrochloride. The tablet can be divided into equal halves.

Methadon HCl Expharma 10 mg is a white or almost white, round, flat bevelled, uncoated tablet scored on one side and imprinted “M10” on the other side. Each tablet contains 10 mg of methadone hydrochloride. The tablet can be divided into equal halves.

Methadon HCl Expharma 20 mg is a white or almost white, hexagonal, uncoated tablet scored on one side and imprinted “M20” on the other side. Each tablet contains 20 mg of methadone hydrochloride. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

The tablets are packed in a clear PVC/PVdC – Alu blister strip or a white HDPE container with HDPE closure.

The excipients are: lactose monohydrate, maize starch, povidone K25 (E1201), colloidal anhydrous silica (E551), talc (E553b), magnesium stearate (E572).

The 5 and 10 mg tablets have a proportional formulation. The 20 mg tablet formulation has slightly different percentages of excipients.

II.2 Drug Substance

The active substance is methadone hydrochloride, an established active substance described in the European Pharmacopoeia. The active substance is soluble in water and freely soluble in 96% ethanol. Methadone hydrochloride is a racemic mixture of enantiomers whereby l-methadone has a higher activity than d-methadone. No polymorphic forms are known.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification is in line with the CEP. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three batches. All three batches comply with the specification.

Stability of drug substance
The active substance is stable for 60 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The goal of the formulation development was to target a stable immediate-release tablet using common excipients and standard manufacturing technology. During formulation studies the following aspects were studied: the influence of hardness on the disintegration time, the influence of different amounts of magnesium stearate and the effect of differences in formulation on the dissolution characteristics. There are two manufacturing processes: one for the 5 and 10 mg strengths and one for the 20 mg strength.

No differences in dissolution characteristics between the products of the two different manufacturing processes are seen. The proposed materials are common and justified on the basis of stability studies. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The product is manufactured using a conventional manufacturing technique of wet granulation followed by direct compression. The manufacturing processes have been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for 3-6 full scale batches per strength.

Control of excipients

The excipients comply with the Ph. Eur. These specifications are acceptable.

Quality control of drug product

The specification of the drug product includes tests for appearance, dimensions, average weight, uniformity of mass, disintegration time, friability, resistance to crushing, identity, assay, degradation, uniformity of dosage units, dissolution and microbiological purity. Methadone can be considered as a BCS class 1 drug and the dissolution limit is set in line with the corresponding requirements in the 'Reflection Paper on Dissolution specification for generic oral immediate release products'. All other proposed limits are also acceptable. The release and end-of-shelf-life limits are identical.

The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on 3 industrial scale batches of each of the 5, 10 and 20 mg strengths, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the drug product has been provided for 21 relevant batches stored at 25°C/60%RH (up to 60 months), 30°/65%RH (12 months) and 40°C/75%RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in a clear PVC/PVdC – Alu blister strip and/or a white HDPE container with white PP cap and/or a white PP container with a white PE cap and/or white HDPE container with a white HDPE cap. Under all storage conditions the drug product remains stable. No specific up- or downward trends are observed. The functionality of the score lines was not evaluated as part of the stability studies. Since no change in hardness is observed during the stability studies, this is not considered necessary.

Based on the results of in-use stability studies, an in-use shelf life of 6 months has been granted after first opening of the HDPE bottle.

The proposed shelf-life for the various combinations of strengths and packaging materials, all without special storage conditions, is justified: 5 years for the blister pack (all strengths) and HDPE bottle pack (10 mg only); 2 years for the HDPE bottle pack (5 mg and 20 mg).

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Methadon HCl Expharma has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

The approval of this product will not result in an increase in the total quantity of the active substances released into the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the MEB agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Methadon is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the MEB agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

The Methadon HCl Expharma tablets exhibit very rapid dissolution (>85% within 15min) over the pH range of 1.2 - 6.8. Considering the average gastric emptying time of 15 min, methadone will reach the intestinal tract as a solution, and as such can be considered comparable to a solution formulation. Moreover, dissolution data at pH 1.2, 4.5 and 6.8 have been provided between Methadon HCl Expharma and for other (generic) tablet formulation, registered in the Netherlands (2), UK (1) and Denmark (1). In all cases dissolution was more than 85% within 15 minutes.
Furthermore, the Methadon HCl Expharma tablets contain no excipients known to affect absorption. Although it can be assumed that the formulations used in literature have different excipients, as methadone is a BCS Class I drug, the influence of excipients on BCS Class I drugs is considered small. Therefore difference in excipients do not have to result in a difference in absorption, besides those known to affect absorption, like sorbitol. However regarding the latter, still for BCS Class I drugs such interactions do not have to result in clinically relevant differences in exposure.
In conclusion, as this is a well established use application, bioequivalence has not explicitly to be proven. As methadone is a BCS Class I drug, the Methadon HCl Expharma formulation does not contain excipients known to affect absorption, and the formulation dissolution is very rapid, in general a comparable bioavailability is expected with regard to the methadone formulation mentioned in the provided literature.

IV.3 Clinical efficacy and safety

In the Netherlands, several methadone products (immediate-release tablets and oral solutions) have been registered for the treatment of severe chronic pain, the treatment of acute withdrawal symptoms in heroin/opiate detoxification, and methadone maintenance therapy (MMT) in harm reduction therapy in heroin dependent patients. In MMT, the patients are treated in outpatients' clinics, with low thresholds regarding continuation of illicit heroin use and harm-reduction as treatment-goal. Methadone is, generally, taken by the addicted patients under supervision. In several treatment centres, stable patients are also allowed to store and use methadone at home.
The use of methadone is considered well-established in the treatment of opioid (heroin) dependence. Form the literature it is evident that MMT is beneficial for harm-reduction regarding HIV-prevention, and improves general health and social functioning in dependent patients. Form randomised trials it is known that higher maintenance doses of 60mg or more are more effective than dosages <40 mg. At higher dosages >100 mg there is a risk of QTc prolongation. According to the Dutch treatment guideline, an ECG should be taken at the start of treatment. In the Dutch clinical practice, methadone has a limited place in treatment of cancer pain. From the literature it is known that methadone is equally effective as other strong opioids like morphine. According to the National guideline on cancer pain, methadone can be considered as an option if morphine is not warranted in chronic pain patients with renal impairment. Because of the risk of accumulation, it is recommended in the guideline to consult an expert.

There is sufficient evidence from the literature that methadone is effective in the treatment of (cancer) pain, and particularly, as a substitution therapy in heroin dependent patients. A main benefit is that methadone could be administered once daily and orally, facilitating outpatient care in dependent patients.
In principle , a waiver to the literature is acceptable from a clinical perspective, given that in studies from the literature, immediate release tablets or solutions were used. Dissolution is not the determining step in absorption and systemic exposure of this drug. Potential variations due to a difference in quality of this product compared to other methadone products used in studies are unlikely to be of clinical relevance, given that a normal dose titration step is 50% of the prior dose, which is generally well-tolerated in clinical practice.
Like all strong opioids, methadone may cause constipation. QTc prolongation has been reported at high dosages. At overdose, ventilatory depression and hypotension occurs.

IV.4 Risk Management Plan

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 Methadon HCl Expharma.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	• QT interval prolongation (including Torsades de Pointes) • Abuse/misuse/dependence • Overdose • Interaction with alcohol • Interactions with CYP 3A4 inhibitors • Renal and liver failure • Intoxication in children
Important potential risks	• Medication errors
Missing information	• Use in pregnancy • Use in children • Use in elderly

The MEB agrees that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.5 Discussion on the clinical aspects

Methadon HCl Expharma is considered widely established. For this authorisation, reference is made to clinical studies and experience with methadone. Methadone hydrochloride has been shown to be effective for:

- Short-term treatment of moderate, severe and very severe pain when no causal treatment is possible.
- Treatment of heroin/opioid withdrawal symptoms during detoxification.

- Maintenance treatment in opioid addicted individuals without a direct abstinence perspective.

The provided clinical overview is sufficient. No new clinical studies were conducted.

V. USER CONSULTATION

The package leaflet (PL) 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 test consisted of a pilot test with 2 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL 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

Methadon HCl Expharma 5 mg, 10 mg and 20 mg tablets has a proven chemical-pharmaceutical quality. Methadon HCl Expharma is an effective drug, which is considered widely established. The benefit/risk balance is considered positive.

The Board followed the advice of the assessors.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated for considered that well established use has been demonstrated for Methadon HCl Expharma, and have therefore granted a marketing authorisation. The national procedure was finalised with a positive outcome on 20 February 2018.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Type of modification	Product Information affected	Date of end of the procedure	Approval/ non approval	Summary/ Justification for refuse