Public Assessment Report

Scientific discussion

Methadon HCl Tiofarma 20 mg, 40 mg and 80 mg, tablets

(methadone hydrochloride)

RVG License Number: 117368, 117370-117371

Date: 19 March 2018

This module reflects the scientific discussion for the approval of Methadon HCl Tiofarma 20 mg, 40 mg and 80 mg, tablets. The procedure was finalised on 2 March 2017. 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
CMS	Concerned Member State
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
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) has granted a marketing authorisation for Methadon HCl Tiofarma 20 mg, 40 mg and 80 mg, tablets, from Tiofarma B.V.

The 20 mg and 40 mg tablets are indicated for:
- moderate, severe and very severe pain, for which no short-term causal treatment is possible;
- treatment of heroin/opioid withdrawal symptoms in view of detoxification;
- maintenance treatment in opioid addicted individuals for whom the abstinence perspective is not appropriate.

The 80 mg tablets are indicated for:
- treatment of heroin/opioid withdrawal symptoms in view of detoxification;
- maintenance treatment in opioid addicted individuals for whom the abstinence perspective is not appropriate.

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

This national procedure concerns a hybrid application claiming essential similarity with the innovator product Symoron 5 mg tablets (NL License RVG 02129) which has been registered in The Netherlands by Astellas Pharma Europe B.V. since 11 April 1990.

The Marketing Authorisation Holder (MAH) has already registered methadon 5, 10 and 20 mg tablets. In this application, next to the introduction of 40 mg and 80 mg strengths, the MAH also applies for a 20 mg strength with a different composition than their previously registered 20 mg tablets. The already approved Methadon HCl 20 mg tablets (RVG 104281) are relatively big (round, diameter of 10 mm). A smaller (oblong, 12 mm in length and a width of 4.5 mm) Methadon HCl 20 mg tablet has been developed to promote patient compliance (ease of swallowing). According to the MAH, Methadone HCl 40 and 80 mg tablets have been developed to improve patient compliance.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, a hybrid application.

Scientific advice
In 2014, the MAH sought a scientific advice from MEB for the products being applied for. The MEB advised that the applications should be submitted as hybrid application (Art. 10.3) with Symoron 5 mg as reference product and the additional strengths 40 and 80 mg as line extensions of the hybrid application. Further, MEB has advised as an alternative to change the composition of the already authorised 20 mg strength via a type II variation, either stand alone or in a grouped submission, including the line extensions.

II. QUALITY ASPECTS

II.1 Introduction

- Methadon HCl Tiofarma 20 mg is a white to off-white oblong tablet inscribed with “MET20” on one side. Each tablet contains 20 mg methadone hydrochloride
- Methadon HCl Tiofarma 40 mg is a white to off-white oblong tablet inscribed with “MET40” on one side. Each tablet contains 40 mg methadone hydrochloride
- Methadon HCl Tiofarma 80 mg is a white to off-white oblong tablet inscribed with “METHADON80” on one side. Each tablet contains 80 mg methadone hydrochloride

The tablets are packed in polypropylene containers with a LDPE cap and/or a 70% LDPE/30% HDPE cap.

The excipients are: lactose monohydrate, magnesium stearate (E572), talc (E553b), sodium starch glycolate type A (E468) and silicified microcrystalline cellulose (E460).

II.2 Drug Substance

The active substance is methadone hydrochloride, an established active substance, described in the European British Pharmacopoeia (Ph.Eur.). It is a white or almost white crystalline powder and soluble in water and freely soluble in ethanol (96%). The active substance is a racemic mixture.

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 European Pharmacopoeia.

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

Quality control of drug substance
The active substance specification is considered adequate to control the quality and is in line with the CEP. It includes additionally tests for residual solvents and microbial purity. Batch analytical data demonstrating compliance with the drug substance specification (except microbial testing) have been provided for two batches from both manufacturers. The batches comply with the proposed set of specifications.

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 product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The choice of the manufacturing process (a straightforward direct compression process) and packaging materials are justified. The MAH performed direct comparison (dissolution profiles) of the products for registration versus reference product Symoron 5 mg. Comparative dissolution data of the products for registration in comparison to those of Symoron 5 mg tablets have been provided. The dissolution data are not fully in accordance with the requirements (pH, volume of the dissolution medium, no individual results reported, different amount of tested units), however this is considered acceptable. The similarity of the dissolution profiles has been demonstrated based on very rapid dissolution.

Manufacturing process
The manufacturing process has been validated according to relevant European guidelines and consists of weighing, mixing and compression. Process validation data on the product have been presented for two batches per strength in accordance with the relevant European guidelines. The product is manufactured using conventional manufacturing techniques.

Control of excipients
The excipients comply with Ph. Eur. requirements. The specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, average mass, uniformity of mass, disintegration, hardness, friability, identification of methadone, identification of chloride, assay, uniformity of content, dissolution, related substances (individual and total) and microbiological purity. Limits in the specification have been justified and are considered appropriate for adequate quality

control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from the proposed production site have been provided on 4 industrial scaled batches of each strength, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided on four small scaled production batches of each strength, stored at 25°C/60% RH (up to 24 months) and 40°C/75% RH (up to 6 months). The conditions used in the stability studies are accordance with applicable European guidelines. All results are within the proposed shelf-life specification. Photostability studies show that the product is sensitive to light. On basis of the data submitted, a shelf life was granted of 30 months with the storage constriction: 'store in the original packaging in order to protect from light'. In-use stability data have been provided demonstrating the product stability for 3 months following first opening of the container. The MAH has committed to perform another in-use stability test at 36 months storage.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Lactose monohydrate is the only excipient of animal origin and compliance with the current TSE Directives 2001/83/EC and EMEA/410/01 rev 2, including Public Statement EMEA/CPMP/571/02 of February 27 2002 and MRFG Report of 27 May 2002 is provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Methadon HCl Tiofarma has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. The following post-approval commitments have been made during the procedure:

- The MAH committed to demonstrate that the applied test methods for microbial purity as included in the drug substance specification are suitable for their use. Demonstration of suitability will be performed as described in Ph. Eur. 2.6.12 and 2.6.13.
- The MAH committed to provide microbial testing results of the first three batches of the drug substance. If it cannot be demonstrated that the material is not supportive of microbial growth, microbiological testing on the drug substance will be performed on routine basis.
- The MAH committed to adapt the statement regarding the frequency of microbiological purity testing of the active substance once the results of the microbiological testing are available.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Methadon HCl Tiofarma is intended for hybrid substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a hybrid formulation of Symoron 5 mg tablets which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. 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

Methadone hydrochloride 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

Biowaiver
In this hybrid application, the MAH has requested a biowaiver of strength for 20, 40 and 80 mg tablet from their own 5 mg tablet (RVG 34508) which was approved based on a BCS-based biowaiver (see page https://db.cbg-meb.nl/Pars/h34508.pdf for public assessment report Methadone HCl Tiofarma 5 mg). It is recognised that according to the Q&A of the PKWP (EMA/618604/2008 Rev. 11, question 13), a biowaiver for additional strengths can be applied only if a bioequivalence study has been performed for one strength. It is however noted that the additional strengths of Methadone HCl Tiofarma (10 and 20 mg tablets) were also accepted based on a biowaiver for the additional strengths with the 5 mg as reference (which was accepted based upon a BCS-based biowaiver). Moreover, in the scientific advice for these newly developed products, a biowaiver for additional strengths based on a BCS-based biowaiver has been considered acceptable. Furthermore, the MAH was able to make a comparison of dissolution data of Methadone HCl Tiofarma with historical data for innovator product Symoron. Although the dissolution data are not fully in accordance with the requirements, this is considered acceptable. Therefore, in this particular case MEB maintains the opinion given in the scientific advice and a biowaiver has been granted.

IV.3 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 Methadone HCl Tiofarma.

- 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 MAO inhibitors, - 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

Additional risk minimisation measures are required to minimise and manage the following risks: medications errors, misuse and abuse. The MAH made a proposal for a PASS study as additional pharmacovigilance for the important identified risks ‘abuse and misuse’ and the important potential risk ‘medication errors’. ‘An observational cohort study of the incidence of medication errors, misuse or abuse of methadone 40 and 80 mg tablets’ versus historical data for the lower strength (5, 10 and 20 mg tablets) will be performed. The MAH will send a survey to the prescribers to obtain information on the incidence of medication errors, abuse and misuse of Methadon HCl 40 and 80 mg tablets. The survey consists of questions for prescribers to collect data on the use of Methadon HCl Tiofarma 40 mg and 80 mg.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Symoron. No new clinical studies were conducted. The MAH demonstrated *in-vitro* that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

Since the package leaflet of the current application is in line with the approved package leaflet of Methadon HCl TioFarma 5, 10 and 20 mg tablets (RVG 34508/104483, 104280 and 104281), it is justified to waive the need for readability testing.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Methadon HCl TioFarma 20 mg, 40 mg and 80 mg, tablets have a proven chemical-pharmaceutical quality and are hybrid forms of Symoron 5 mg tablets. Symoron is a well-known medicinal product with an established favourable efficacy and safety profile.

No comparative bioavailability or bioequivalence study was carried out. Instead, reference was made to fulfilling all requirements for a biowaiver. This has been sufficiently demonstrated.

In the Board meeting of 28 July 2016 , the following was discussed: Additional data was needed by the board in order to accept an application based on *in-vitro* data alone. The MAH provided these data and therefore, the issue was resolved.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated for Methadon HCl Tiofarma with the reference product, and has therefore granted a marketing authorisation. The national procedure was finalised with a positive outcome on 2 March 2017.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse