

**PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands**

**Methadon HCl TioFarma 10 mg and 20 mg, tablets
TioFarma b.v., the Netherlands**

methadone (as hydrochloride)

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB.

It reflects the scientific conclusion reached by the MEB at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.

This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

Registration number in the Netherlands: RVG 104280-104281

14 November 2012

Pharmacotherapeutic group:	drugs used in addictive disorders, drugs used in opioid dependence
ATC code:	N07BC02
Route of administration:	oral
Therapeutic indication:	moderate to severe pain; heroin/opioid withdrawal symptoms; maintenance treatment in opioid addiction.
Prescription status:	prescription only
Date of authorisation in NL:	26 April 2010
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board of the Netherlands (MEB) has granted a marketing authorisation for Methadon HCl TioFarma 10 mg and 20 mg, tablets from TioFarma b.v. The date of authorisation was on 26 April 2010 in the Netherlands.

The product is indicated for:

- Use as an analgesic in moderate to severe pain when no 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.

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

Methadone is a strong opioid agonist with actions predominantly at the μ receptor. The analgesic activity of the 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 with pA_2 value similar to its anti-antagonism of morphine. 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.

The national procedure concerns a line extension to Methadon HCl TioFarma 5 mg tablets (NL License RVG 34508), which has been registered in the Netherlands since 2 June 2008. The 5 mg product authorised as a generic form of Symoron 5 mg tablets (NL License RVG 02129), which has been registered in the Netherlands by Astellas Pharma B.V. since 11 April 1990.

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product.

The current application does not include a comparative bioavailability or bioequivalence study, but reference is made to fulfilling all requirements for a biowaiver. See paragraph II.3 "Clinical Aspects". This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice

The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance

The active substance is methadone hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance a white, crystalline powder, which is soluble in water and freely soluble in acetone.

The CEP procedure is used for both suppliers of 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 drug substance specification is in line with the Ph. Eur. and the CEPs. The specification is acceptable in view of the route of synthesis and the various European guidelines.

Batch analytical data demonstrating compliance with the drug substance specification have been provided.

Stability of drug substance

Stability data on the active substance have been provided for the drug substance manufactured by one of the suppliers for 7 full-scale batches stored at 25°C/60%RH (up to 60 months), 40°C/75%RH (6 months) and 30°C/65%RH (6 months). The retest period as proposed was considered acceptable: 60 months, store protected from light.

The active substance from the other manufacturer is stable for 3 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

* *Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition

Methadon HCl TioFarma 10 mg and 20 mg are white to off-white round tablets. The 10 mg tablets have a diameter of 8 mm and are on one side embossed with "methadon 10". The 20 mg tablets have a diameter of 10 mm and are on one side embossed with "methadon 20".

The tablets are packed in PVC/Alu blister packaging in a cardboard box or in polypropylene flacon with LDPE closure.

The excipients are: lactose, magnesium stearate (E572), talc, sodium starch glycollate type A, silicified microcrystalline cellulose.

The 10 mg and 20 mg tablets are weight proportional to the 5 mg tablets.

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The starting formulation was based on experience with other direct compression mixtures. The (amount of) excipients were selected to obtain comparable dissolution profiles with the innovator product.

The line extension products differ only in the strength and size of the tablets compared to the approved 5 mg product. The granulate is qualitatively and quantitatively identical for all products. Dissolution characteristics are the same for all three strengths and dissolution is fast. Therefore a difference in bio-availability is not expected.

The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The ingredients are mixed and finally a lubricant is added. This blend is mixed until homogeneity is obtained and compressed into tablets. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full-scale batches.

Control of excipients

The excipients comply with the Ph. Eur., where applicable. The specifications for ProSolve (silicified microcrystalline cellulose) are based on the Ph. Eur. as well as the pharmacopoeias of the USA and Japan. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for appearance, disintegration time, mean weight, uniformity of mass, diameter, thickness, hardness, friability, identification (methadone hydrochloride and chloride), assay, related substances, uniformity of content, microbial quality and dissolution test.

The release and shelf life specifications are acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production sites have been provided on three full-scale batches, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided on three production-scale batches of each strength stored at 25°C/60% RH (6 months) AND 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The tablets were stored in PVC/Alu-blisters with transparent PVC film and also in polypropylene containers with a low density polyethylene (LDPE) closure. The latter is considered to be just for informative purpose. No significant changes were observed under long-term conditions, but at accelerated conditions the tablet hardness decreases significantly and out-of-specification results are observed. Based on the fact that the granulate is common (quantitatively and qualitatively) for all strengths, the same trends are observed for all tablet strengths. As a shelf-life of 24 months has also been accepted for the 5 mg tablets, a shelf-life of 24 months when stored below 25°C is justified for the 10 mg and 20 mg strengths as well.

A commitment to provide additional stability data to cover the proposed shelf-life of 24 months was made.

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

Lactose is derived from healthy animals in the same conditions as milk collected for human consumption. Magnesium stearate is derived from plant material was also included.

II.2 Non clinical aspects

This product is a line extension to Methadon HCl TioFarma 5 mg tablets, which is available on the European market. 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 Board agreed that no further non-clinical studies are required.

Environmental risk assessment

The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of methadone released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Methadone 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 Board agreed that no further clinical studies are required.

Biowaiver

For this line extension, no bioequivalence study was conducted. Reference is made to the biowaiver granted for Methadon HCl TioFarma 5 mg (NL License RVG 34508). For this product a Public Assessment Report (PAR) is available on the MEB website. This is acceptable, as the following criteria are met:

- Methadone absorption is high (90%) and dose dependant.
- The three tablet strengths are dose proportional.
- The different strengths are manufactured by the same process and by the same manufacturer.
- Comparative dissolution data at three different pH values show comparable dissolution.

Risk management plan

Methadone was first approved in 1990, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of methadone can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC

The content of the SPC approved during the national procedure is in accordance with that accepted for the reference product and with other generic methadone products.

Readability test

The package leaflet has not been evaluated via a user consultation study. Reference is made to the successful user test for Methadon HCl TioFarma 5 mg, tablets. This is acceptable.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Methadon HCl TioFarma 10 mg and 20 mg, tablets have a proven chemical-pharmaceutical quality and are an approvable line extension to Methadon HCl TioFarma 5 mg tablets. Methadon HCl TioFarma 5 mg was registered on as a generic form of Symoron 5 mg tablets on 2 June 2008.

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.

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

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other methadone containing products.

The Board followed the advice of the assessors. The MEB, on the basis of the data submitted, considered that Methadon HCl TioFarma 10 mg and 20 mg are legitimate line extensions to Methadon HCl TioFarma 5 mg, and has therefore granted a marketing authorisation. Methadon HCl TioFarma 10 mg and 20 mg, tablets were authorised in the Netherlands on 26 April 2010.

The following post-approval commitment has been made during the procedure:

Quality - medicinal product

- The MAH committed to provide additional stability data to cover the proposed shelf-life of 24 months

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C _{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
t _{1/2}	Half-life
t _{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached