CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Methadon HCl TioFarma 5 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 34508

16 June 2010

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:	2 June 2008
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 5 mg, tablets from TioFarma b.v. The date of authorisation was on 2 June 2008 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.

This national procedure concerns a generic 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 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, normally 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 new 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 25ºC/60%RH (up to 60 months), 40ºC/75%RH (6 months) and 30ºC/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 5 mg is a white, round tablet with a diameter of 6 mm.

The tablets are packed in unit dose packs containing transparant PVC/Alu-blisters with 50 dosage units or 5 tablets per blister.

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

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 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 three full-scale batches stored at 25ºC/60%RH (24 months) and 40ºC/75%RG (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The tablets were stored in PVC/Aluminium blisters.
Significant change is observed in hardness in the tablets stored at 40ºC. It is acceptable that no studies are performed at 30ºC since it is unlikely that other parameters than hardness will change. The product was shown to be stable with respect to light. Based on the data provided, a shelf life of 24 months was granted. The product should be stored below 25ºC.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Only lactose and magnesium stearate have a possible risk of transmitting TSE. Lactose is derived from healthy animals in the same conditions as milk collected for human consumption. Magnesium stearate is derived from plant material.

II.2 Non clinical aspects

This product is a generic formulation of Symoron, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

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

Bioequivalence/ Waiver
In order to obtain a biowaiver, an extensive expert report was submitted to support this application.

Reference is made to *Relating issues* in the *Note for Guidance on the investigation of bioavailability and bioequivalence.*
See below the arguments of the MAH for a biowaiver for Methadon HCl TioFarma 5 mg, tablets:

A) Characteristics related to the active substance
a.i. Risk of therapeutic failure or adverse drug reactions
Reference is made to literature indicating that methadone tolerance is significantly higher in opioid-dependent patients and patients suffering from pain compared to healthy subjects.

a. ii. Risk of bio-inequivalence
A bioequivalence study was initiated, but cancelled after period I, as a number of the healthy, opioid-naive subjects enrolled experienced symptoms of overdose. The data obtained in period I were submitted to support the application. The pharmacokinetic parameters of test and reference products were demonstrated to be comparable (see table).

PHARMACOKINETICS

Pharmacokinetic parameters of treatments R and T (mean ± SD)

		Treatment R			Treatment T		
Parameter	Unit	N	Mean	SD	N	Mean	SD
C_{max}	ng/mL	12	38.8	9.65	12	43.0	10.8
t_{max}	h	12	2.25	0.65	12	2.21	0.94
AUC_t	ng.h/mL	12	1205	268	12	1251	348
AUC_∞	ng.h/mL	12	1554	390	12	1623	577
$t_{½}$	h	12	44.65	11.39	12	44.38	16.32

R= Symoron, T= Methadon HCl TioFarma 5 mg

Moreover, reference is made to a double-blind study by Gourevitch (J Subst abuse Treat 1999; 17(3): 237-41), patients on methadone maintenance therapy received three different US methadone formulations (tablets, liquid and diskets) in a randomised way. There were no significant differences in pharmacokinetic profile and pharmacodynamic effect of the different products.

a.iii. Solubility
The so-called dose number - defined as the mass divided by the product of uptake volume (250 ml) and solubility of drug - for methadone is 0.0045, which indicates high solubility in water. The Merck Index also states that methadone is highly soluble.

a.iv. Pharmacokinetic properties
From literature it is known that the bioavailability of methadone is linear and high (80-90%). A number of references is included in support of this statement.

B) Characteristics related to the medicinal product
b.i. Rapid dissolution
Dissolution studies were conducted with a batch of 5000 tablets. Dissolution profiles at pH 1.0, 5.5 and 6.8 were investigated against the reference product Symoron. The solution was analysed after 5, 15, 30 en 45 minutes. Methadone HCl TioFarma and Symoron were shown to have similar dissolution profiles. Methadone HCl dissolves easily in aqueous environment at pH 1.0, 5.5 and 6.8 (approximately 100% methadone is dissolved after 5 minutes), thus dissolution is not a limiting factor for absorption.

b.ii. Excipients
The excipients included in the composition of the medicinal product are well established and no interaction with the pharmacokinetics of the active substance is expected. The excipients are considered not to effect absorption or pharmacokinetics of methadone.

b.iii. Manufacture

It is unlikely that particle size and polymorphism will influence the physiochemical and biological properties since methadone HCl dissolves easily in aqueous environment. The manufacturing process has been further assessed and approved of from a quality point of view.

Conclusion bioequivalence / biowaiver

As methadone is considered highly permeable and well absorbable, and dissolution and solubility are considered non-problematic, a waiver can be granted. A bioequivalence study was initiated, but discontinued for ethical reasons. The risk of bio-inequivalence compared with Symoron is unlikely, as was demonstrated through results of the study as well as by literature data.

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 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 two rounds with 10 participants each. The respondent group had an adequate distribution of the parameters sex, age and education. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. After the diagnostic test, an assessment of layout and content was performed.

As several subjects experienced difficulty in understanding one item, the underlined sentence “Do not use more than your doctor told you.” has been added, to stress that patients should always consult their doctor before changing the dose. This revision is acceptable and resulted in better results on this question in the second test round.

In total, thirteen items have been presented to the respondents with respect to the ability to find and understand the information. For every item, it has been evaluated to what extent these thirteen items could be found in the PIL. It was shown that 97% of the items could be found (from both the first and the second test round). Also for every item, it has been tested to what extent the respondents were able to understand the information. Almost all respondents could interpret the messages in the package leaflet correctly (94%). The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Methadon HCl TioFarma 5 mg, tablets has a proven chemical-pharmaceutical quality and is a generic form 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.

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 essential similarity has been demonstrated with the reference product, and has therefore granted a marketing authorisation. Methadon HCl TioFarma 5 mg was authorised in the Netherlands on 2 June 2008.

There were no post-approval commitments made during the procedure.

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
$t_{½}$	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