PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands

Methadon Regenboog 5 mg, 10 mg and 20 mg, tablets
Regenboog Apotheek Bavel BV, 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 33034-33036

24 August 2010

Pharmacotherapeutic group: drugs used in addictive disorders, drugs used in opioid dependence
ATC code: N07BC02
Route of administration: oral
Therapeutic indication: heroin/opioid withdrawal symptoms; maintenance treatment in opioid addiction.
Prescription status: prescription only
Date of authorisation in NL: 20 September 2007
Application type/legal basis: Directive 2001/83/EC, Article 10(1)a

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 Regenboog 5 mg, 10 mg and 20 mg, tablets from Regenboog Apotheek Bavel BV. The date of authorisation was on 20 September 2007 in the Netherlands.

The product is 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 SPC.

Methadone is a strong opioid agonist with actions predominantly at the $\mu$ 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 $\kappa$ and $\delta$ 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 bibliographical application. In addition, reference is made to 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. According to the SPC the dosage for maintenance treatment is usually 50-100 mg. The application for a line extension of the 5 mg tablets to 10 and 20 mg strengths is therefore acceptable.

The marketing authorisation is granted based on article 10(1)a 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 biowaver. See paragraph II.3 “Clinical Aspects”. These products 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 these product types 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 is a white, crystalline powder, which is soluble in water and freely soluble in acetone.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or ‘know-how’ of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The manufacturing process of the drug substance has been sufficiently described. The starting materials and reagents are adequately controlled.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. The analytical procedures are considered appropriate. Batch analytical data on 6 production-scale batches have been provided. All presented batches comply with the specifications set.

Stability of drug substance
Stability data on the active substance have been provided for 3 batches stored at 25°C/60% RH (24-36 months) and 40°C/75% RH (6 months). No out of specifications were observed. Based on the data submitted, a retest period could be granted of 36 months. No special storage conditions are required.

* 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
The products are round, biconvex tablets with a diameter of 8.8 mm and break-mark on one side.

Methadon Regenboog 5 mg is white, the 10 mg tablet is yellow and the 20 mg product is green. The tablets can be divided into equal halves.

The tablets are packed in white polypropylene (PP) containers.

The excipients are: lactose, microcrystalline cellulose (E460), talc (E553b), magnesium stearate 10 mg only - quinoline yellow(E104), aluminium oxide 20 mg only - tartrazine (E102), indigo carmine (E132), aluminium oxide.

The contents of the excipients are the same for all the tablets with a minor deviation of the content of lactose to compensate for the difference in active substance.
Pharmaceutical development
The choice of excipients has been sufficiently justified. All excipients are commonly used. No requirement for particle size was laid down because of the solubility of methadone hydrochloride and the rapid dissolution of the tablets. The Ph.Eur. requires a release of at least 75% within 45 minutes in water. The solubility of methadone hydrochloride as well as the dissolution of the tablets are very fast (> 85% in 15 minutes). The pharmaceutical development has been sufficiently performed and explained.

Manufacturing process
The manufacturing process consists of sieving, mixing and compression. The process has been validated for three production-scale batches, one of each strength. Process validation on additional full-scale batches will be performed post authorisation.

Control of excipients
Lactose, cellulose, talc and magnesium are controlled in accordance with the corresponding Ph.Eur. monographs. These specifications are acceptable. For the colourants acceptable specifications have been laid down.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage and include tests for appearance, mass, uniformity of mass, uniformity of mass of tablet halves, uniformity of dosage, disintegration, resistance to crushing of tablets (hardness), friability, microbial contamination, identification tests, assay, dissolution and related substances. Satisfactory validation data for the analytical methods have been provided. Breakability of the tablets has been sufficiently investigated. Batch analytical data from 3 full-scale batches of each strength have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for 3 full-scale batches of each strength stored at 25°C/60% RH and 40°C/75% RH for up to 36 months. Storage during exposure to light from a cool white fluorescent lamp was also studied. The tablets were stored unpacked (in open container) or in the proposed package, i.e. polypropylene containers. The results suggest that the tablets should be stored in closed containers. Based on the stability data provided, a shelf life of 3 years could be granted. The product should be stored below 25 ºC in the original package to protect from light and moisture.

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.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 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 Regenboog 5 mg, tablets:

A) Characteristics related to the active substance

a.i. Risk of therapeutic failure or adverse drug reactions
When this product would be approved, more than one methadone tablet formulation will be available at the Dutch market. It could not be excluded that the registered product Symeront® and the product to be registered will be interchanged. The new methadone product is not tested for bioequivalence. If the products are not bioequivalent, this may lead to withdrawal symptoms or symptoms of overdose when patients switch from one product to the other.

The MAH submitted however some relevant literature where the therapeutic window of methadone is discussed:

a) In 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 PK profile and PD effect of the different products.

b) In a study by Curran et al (Addiction (1999) 94(5), 665-674), a 33% increase in methadone dosage did not lead to adverse events. Moreover, the addicted patients on maintenance therapy from this study were not able to distinguish a 33% increase of methadone from placebo.

c) In a study by Inturrisi et al. (CPT 1987;41:392-401) it became clear that the PK-PD relation between methadone plasma values and pain reduction was broad in patients with chronic pain (effective value varied from 0.04-1.13 µg/ml).

These data indicate that methadone is not a narrow therapeutic drug, and that the consequences of bio-inequivalence of Methadone Regenboog tablets compared to reference products may be limited in clinical practice.

a. ii. Risk of bio-inequivalence
The MAH states that the risk of bio-inequivalence is negligible, as methadone has very high solubility. Gourevitch detected no significant difference in AUC between immediate release tablets, oral drops and orodispersible tablets in a range of 30-100 mg. There is no evidence that bioavailability or bioequivalence problems exist for methadone products.

a.iii. Solubility
According to the guidelines, the active substance is considered highly water soluble if the amount contained in the highest dose strength is dissolved in 250 ml of each of the three buffers within the range of pH 1-8 at 37 °C. Assuming a maximal dose of 100 mg, the dose number of methadone is far below 1 (< 0.0002).

a.iv. Pharmacokinetic properties
In literature submitted by the MAH, bioavailability of methadone HCl was estimated as 85-95%. These data indicate that the absorption of methadone is indeed high, although not complete. Literature data were provided, confirming dose linearity (Wolf et al., Clin Chemm 1991). Methadone plasma levels and dose were highly correlated (R= 89%) in patients treated with 5-100 mg methadone.

B) Characteristics related to the medicinal product

b.i. Rapid dissolution
The MAH submitted data demonstrating that the test tablets (Methadone HCl Regenboog 5,10 and 20 mg) and the reference product are both rapidly dissolved in water (dissolution was >92% within 10 minutes for all tested products). All tablets strengths were dissolved > 90% within 10 minutes under each pH condition, for both the test and reference formulation.

b.ii. Excipients
The test product does not contain excipients which may interfere with absorption of the active substance. As the test product contains only small amounts of magnesium stearate, it is not expected that this would largely influence absorption of the active compound.

**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. The risk of bio-inequivalence compared with Symoron is unlikely, as was demonstrated 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 post authorisation 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 SPC was brought in accordance with the latest version of Pinadone methadone oral solution (MRP NL/H/0618/001, RVG 24296).

**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 questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The readability test has been sufficiently performed.
III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Methadon Regenboog 5 mg, 10 mg and 20 mg, tablets have a proven chemical-pharmaceutical quality and are generic forms of Symoron 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 Regenboog 5 mg, 10 mg and 20 mg, tablets were authorised in the Netherlands on 20 September 2007.

There were no post-approval commitments made during the procedure.
## List of abbreviations

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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ASMF</td>
<td>Active Substance Master File</td>
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<tr>
<td>ATC</td>
<td>Anatomical Therapeutic Chemical classification</td>
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<td>AUC</td>
<td>Area Under the Curve</td>
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<td>BP</td>
<td>British Pharmacopoeia</td>
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<td>CEP</td>
<td>Certificate of Suitability to the monographs of the European Pharmacopoeia</td>
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<tr>
<td>CHMP</td>
<td>Committee for Medicinal Products for Human Use</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Maximum plasma concentration</td>
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<tr>
<td>CMD(h)</td>
<td>Coordination group for Mutual recognition and Decentralised procedure for human medicinal products</td>
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<tr>
<td>CV</td>
<td>Coefficient of Variation</td>
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<td>EDMF</td>
<td>European Drug Master File</td>
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<td>EDQM</td>
<td>European Directorate for the Quality of Medicines</td>
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<td>EU</td>
<td>European Union</td>
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<td>GCP</td>
<td>Good Clinical Practice</td>
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<td>GLP</td>
<td>Good Laboratory Practice</td>
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<td>GMP</td>
<td>Good Manufacturing Practice</td>
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<td>ICH</td>
<td>International Conference of Harmonisation</td>
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<td>MAH</td>
<td>Marketing Authorisation Holder</td>
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<td>MEB</td>
<td>Medicines Evaluation Board in the Netherlands</td>
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<td>OTC</td>
<td>Over The Counter (to be supplied without prescription)</td>
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<td>PAR</td>
<td>Public Assessment Report</td>
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<td>Ph.Eur.</td>
<td>European Pharmacopoeia</td>
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<td>PIL</td>
<td>Package Leaflet</td>
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<td>PSUR</td>
<td>Periodic Safety Update Report</td>
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<td>SD</td>
<td>Standard Deviation</td>
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<td>SPC</td>
<td>Summary of Product Characteristics</td>
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<tr>
<td>t&lt;sub&gt;½&lt;/sub&gt;</td>
<td>Half-life</td>
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<tr>
<td>t&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Time for maximum concentration</td>
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<td>TSE</td>
<td>Transmissible Spongiform Encephalopathy</td>
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<td>USP</td>
<td>Pharmacopoeia in the United States</td>
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### STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

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<th>Scope</th>
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<th>Date of start of the procedure</th>
<th>Date of end of the procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
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