CBG MEB

Public Assessment Report

Scientific discussion

Eptadone Drank Suikervrij 1 mg/ml, 5 mg/ml and 10 mg/ml, oral solution

(methadone hydrochloride)

NL License RVG: 111793, 111803, 111804

Date: 24 September 2015

This module reflects the scientific discussion for the approval of Eptadone Drank Suikervrij. The marketing authorisation was granted on 12 September 2014. For information on changes after this date please refer to the module 'Update'.

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 *Eptadone Drank Suikervrij* 1 mg/ml, 5 mg/ml and 10 mg/ml, oral solution from L. Molteni & C. dei F.LLi Alitti Soceità di Esercizio S.p.A.

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 SmPC.

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 pA2 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 line extension of Eptadone® (methadone) oral solution, with sugar-free 1, 5 and 10 mg/ml oral solutions. Currently, Eptadone® 1 and 5 mg/ml sugar-containing solutions (NL License RVG 31539-31540, registered since 2006) are marketed. No 10 mg/ml solution is yet available.

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC, a bibliographic application based on well-established use of methadone.

II. QUALITY ASPECTS

II.1 Introduction

Eptadone Drank Suikervrij 1 mg/ml is a clear, green coloured syrupy liquid with cherry taste.
Eptadone Drank Suikervrij 5 mg/ml is a clear, light amber syrupy liquid with cherry taste.
Eptadone Drank Suikervrij 10 ml/ml is a clear, blue coloured syrupy liquid with cherry taste.

The oral solution is packed in 100 ml, 500 ml and 1000 ml amber transparent non-plasticised PVC bottles, closed with a polypropylene/polyethylene screw cap fitted with a polyethylene (EPE) liner. A measuring device is provided with the bottles.

The excipients are xylitol, glycerol, sodium benzoate, citric acid monohydrate, hydroxyethylcellulose, cherry flavour, purified water and colourants (caramel in 5 mg/ml, tartrazine in 1 mg/ml and brilliant blue in 1 mg/ml and 10 mg/ml).

II.2 Drug Substance

The active substance is methadone hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is soluble in water, ethanol and isopropanol and practically insoluble in ether and glycerol. The molecule contains one asymmetric carbon atom and is present as the racemate. There is no evidence of polymorphism of methadone in literature.

The CEP procedure is used for both manufacturers 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
CEPs have 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, with some additional requirements. 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 for three full-scale batches of each CEP holder.

Stability of drug substance
The active substance is stable for 3 years from one supplier, or 60 months for the second CEP holder. 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 products are the sugar-free version of already registered methadone oral solutions, containing xylitol and glycerol as sweeteners. The solution should have a high viscosity to prevent injection of this oral solution. The flavour has been chosen to mask the bitter taste of the active substance. Colouring is based on other registered products and is green for the 1 mg/ml solution, amber for the 5 mg/ml product and blue for the 10 mg/ml product. A preservative is considered necessary as it is an aqueous solution. The preservative effect has been adequately shown. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process consists of dissolving the excipients to obtain a ‘placebo solution’, followed by addition of the active substance. This solution is filled into bottles and packaged in carton boxes. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for two pilot-scaled batches of each strength. The product is manufactured using conventional manufacturing techniques. Process validation for full scaled batches will be performed post authorisation.

Control of excipients
The excipients comply with Ph.Eur. requirements, except the cherry flavor and the colourants which comply with in-house specifications. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for characteristics, appearance, density, pH, viscosity, colourant identification, methadone identification, sodium benzoate identification, methadone content, sodium benzoate content, related substances, Total aerobic microbial count (TAMC), Total combined yeasts/mould count (TYMC), E.coli, uniformity of dosage units or of multidose containers and average volume. The shelf-life specification is identical to the release specification with the exception of lower limit of viscosity. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on one laboratory scaled and two pilot-scale batches of each strength, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided on one laboratory scaled and two pilot-scale batches of each strength stored 25°C/60% RH (up to 36 months) and 40°C/75% RH (up to 6 months). The

conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in non-plasticized PVC bottles 100 ml/500 ml/1000 ml. The shelf-life period of 36 months is considered acceptable. The results of a photostability study show that the product should be stored protected from light (100 ml and 500 ml bottles only).

An in-use stability test was carried out on the 100 ml and 1000 ml bottles. One batch was tested at the beginning of the stability study and another one at the end of the study. The data show that the product remains stable for 12 months following first opening of the container.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

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

The following post-approval commitments were made:
- The MAH committed to repeat the validation study on the first three industrial batches according to the same protocol used for pilot batches.
- The MAH committed to repeat the in-use stability test with batches at the end of shelf-life.
- The MAH committed to repeat long term and accelerated stability studies, including the water loss test, on the first industrial batches, according to the same stability protocol used for development batches.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since *Eptadone Drank Suikervrij* is a substitute for other methadone products on the market, 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

The use of methadone is well-established. 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 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 for this line extension.

The MAH provided justification for the introduction of a sugar free Eptadone formulation, and applied for a biowaiver.

IV.2 Pharmacokinetics

Biowaiver
The MAH requested an exemption from bioequivalence studies. The differences in the composition between the sugar-containing and sugar-free formulations were assessed.

The 1 mg/ml, 5 mg/ml and 10 mg/ml sugar-free formulations have the same quantitative and qualitative composition with an exception of colouring agents which is not expected to have any clinical consequences. The solutions can be considered similar, as the total amount of active substance is less than 5% of the excipients in 1 ml solution. There is a lack of clear evidence for linearity in pharmacokinetics of methadone. However, since there is a high inter- and intraindividual variability in the pharmacokinetics of methadone, an uptitration from the initial 20 mg dose is based on the individual patient response. Moreover, methadone has a wide therapeutic index and therefore the additional higher concentration is also acceptable.

Hydroxyethylcellulose is present in the sugar-free solution. This thickening agent is not known to have any effects on gastrointestinal transit, absorption, solubility or stability of methadone. The difference in flavouring/colouring agents is not expected to affect the absorption of methadone either.

However, the addition of xylitol and removing sucrose from the formulation may be expected to cause differences in the absorption of methadone from the two formulations.
Xylitol, a sweetening agent, may have laxative effect in quantities greater than 10 g/day (Excipients in the label and package leaflet of medicinal products for human use, Notice to Applicants Volume 3B, July 2003). The maximum recommended daily dose of methadone is 100 mg (in the maintenance therapy) which would result in 10 g daily intake of xylitol when given as the 1 mg/mg presentation, which is the limit. Moreover, in clinical practice, methadone may be given even up to 120 mg/day which would result in the ingestion of 12 g of xylitol. As such, due to laxative effects, the absorption of methadone can be affected. It is therefore recommended to use 5 mg/ml or 10 mg/ml formulation when a daily dose of 100 mg of Eptadone is needed. This will result in daily xylitol intake of 1 or 2 g, which is far below the laxative threshold. The applicant should include the following wording in section 4.2 of the SmPC:

When daily dose of 100 mg of Eptadone is needed, it is recommended to use 5 or 10 mg/ml presentation in order to avoid possible laxative effects of xylitol, which could occur with the use of 1 mg/ml sugar-free formulation at 100 mg dose..

Sucrose has been left out in the new formulation. Taken into account the maximum daily dose of 100 mg which is also maximum single dose for methadone and using the 1 mg/ml solution, a dose of 40 g sucrose may be applied. Sucrose is not absorbed from the (healthy) gastro-intestinal tract, but is hydrolysed in the small intestine by the enzyme sucrase to glucose and fructose, which can be absorbed. Sucrose can decrease the rate of gastric emptying, and possibly delay absorption of some drugs. However, it is not clear at which concentration this occurs. In addition, large differences are observed in the individual response to sucrose with respect to gastric emptying. Questions were asked whether the absorption of methadone can be affected in the new formulation.
The MAH referred to a study by Barker et al. (1974), in which the effect of glucose and potassium chloride on a rate of gastric empting was evaluated. From this study it can be concluded that decrease in gastric empting progressed with increasing osmolarity up to 1000 mOsm/L. There appeared to be a ceiling effect with osmolarities of a solute above 1000 mOsm/L: little or no decrease in gastric empting was observed. As presented by the MAH, the osmolarities of Eptadone and Eptadone sugar-free formulations range between 2277 – 2301 and 1766 – 1818 mOsm/L, respectively. Therefore, it can be assumed that the effect of the two formulations of Eptadone on gastric empting and thus on an absorption of methadone will be not an issue.

IV.3 Clinical safety

The MEB considers that marketing of a sugar-free formulation can be supported, as opioid dependent patients often have a poor dental health, as a consequence of life-style, and because opioids reduce saliva production in the oral cavity.
The 10 mg/ml concentration allows smaller volumes of high doses. On one hand, this is considered a benefit, as in current clinical practice, high doses are applied (40-100 mg) as maintenance therapy.

Smaller volumes may be more acceptable for the patient, and the intake of smaller volumes may be better controllable in supervised settings.

However, on the other hand, the introduction of a higher concentration also includes a risk of dosing errors. With the 10 mg/ml strength, patients receive a double to tenfold dose if accidently the same volume is applied as for the 1 or 5 mg/ml formulation, and this may cause overdose and even fatalities. If patients are converted to the 10 mg/ml strength and receive a considerable smaller volume than usual without further explanation and guidance, there may be a risk of reduced efficacy and disadherance, and increment of illegal drug use. The concerns are sufficiently addressed by the MAH by means of the Risk Management Plan and a Post-authorisation Safety Study (PASS).

IV.4 Risk Management Plan

The RMP submitted by the MAH is 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 *Eptadone Drank Suikervrij.*

Table 1. Summary of safety concerns relating to the active substance

Summary of safety concerns	
Important identified risks	1. Respiratory depression 2. Cardiac diseases (in particular cardiac arrhythmias) 3. Overdose 4. Pregnancy 5. Breastfeeding
Important potential risks	6. Possible risk of medication errors 7. Abuse 8. Misuse
Important missing information	None

Educational material will be distributed to healthcare professionals involved in the prescription and distribution of the new methadone strength 10 mg/ml in order to aim at risk minimisation and to support safe and effective use for the product.

The MEB directed the MAH to prepare a PASS protocol. The study design laid down by the MAH is a prospective observational cohort multicentre study with a control cohort with retrospective collection of data. Approximately 400 opioid dependent patients treated with Eptadone solution will be prospectively observed in about 20 sites. Data of approximately 200 patients treated with alternative methadone maintenance treatment will be collected retrospectively (control group). Alternative treatment includes all methadone maintenance treatments (dosage and form) available on the market in the Netherlands.

The primary objective is to capture and evaluate additional safety aspects in terms of medication errors, misuse, abuse and overdose of *Eptadone Drank Suikervrij* 10 mg/ml oral solution during a period of 2 years.
The secondary objectives are to better define the safety profile and drug utilisation of the 10 mg/ml oral solution and to obtain retrospective data from patients undergoing alternative methadone treatment for opioid addiction.

Table 2. Required additional pharmacovigilance activities

	Description of activity (or study title if known)	Milestone(s)	Due Date(s)
PASS (MOLT-2013-03)	A prospective observational cohort study, including an additional retrospective control cohort, to assess the incidence of medication errors, misuse, abuse and overdose in opioid-addicted patients administered with Eptadone® DRANK SF 10 mg/ml oral solution as methdone maintenance treatment	1.MEB Protocol submission	28 May 2014
		2.Start of data collection	I Q 2015
		3. End of data collection	II Q 2017
		4. Final report of study results	I Q 2018 (as per GVP Module VIII the final report will be submitted to the Competent Authority of the Member State in which the study was conducted as soon as possible within 12 months of the end of data collection).

The protocol is considered appropriate to investigate the primary and secondary objectives, and to address the important potential risks.

IV.5 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with Eptadone® 1 mg/ml and 5 mg/ml (sugar-containing) oral solution. The MAH sufficiently justified that a bioequivalence study is not required, and that the excipients in the sugar-free formulation are not expected to affect the absorption of methadone. Risk management is adequately addressed.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Eptadone Drank Suikervrij 1 mg/ml, 5 mg/ml and 10 mg/ml, oral solution have a proven chemical-pharmaceutical quality and is an approvable line extension to Eptadone 1 mg/ml and 5 mg/ml oral solution. The sugar-containing Eptadone formulation is a well-known medicinal product with an established favourable efficacy and safety profile.

A biowaiver was granted, as the differences between the current and new formulations are justified and will not affect pharmacokinetics.

The 10 mg/ml formulation concerns a new, higher strength. The MAH sufficiently addressed the concerns regarding medication errors, misuse, abuse and overdose by means of the Risk Management Plan and a Post-authorisation Safety Study (PASS).

The Board followed the advice of the assessors. The MEB, on the basis of the data submitted, considered that efficacy and safety has been shown, and has therefore granted a marketing authorisation. *Eptadone Drank Suikervrij* oral solution was authorised in the Netherlands on 12 September 2014.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

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