Public Assessment Report

Decentralised Procedure

Misyo 10 mg/ml concentrate for oral solution

(methadone hydrochloride)

UK/H/5165/001/DC

UK licence no: PL 40168/0001

INN-FARM d.o.o.

Medicines and Healthcare Products Regulatory Agency

Misyo 10 mg/ml concentrate for oral solution

PL 40168/0001

LAY SUMMARY

On 19th August 2013, the Medicines and Healthcare products Regulatory Agency (MHRA) granted a Marketing Authorisation (licence) to INN-FARM d.o.o. for the medicinal product Misyo 10 mg/ml concentrate for oral solution (PL 40168/0001; UK/H/5165/001/DC). This medicine is only available on prescription from the doctor.

This medicine contains methadone hydrochloride, which belongs to a group of medicines called narcotic analgesics. It is used in the treatment of addiction in order to reduce withdrawal symptoms.

All patients receiving Misyo must be routinely monitored for signs of misuse, abuse and addiction during treatment.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Misyo 10 mg/ml concentrate for oral solution outweigh the risks; hence a Marketing Authorisation was granted.

TABLE OF CONTENTS

Module 1
Information about initial procedure

Product Name	Misyo 10 mg/ml concentrate for oral solution
Type of Application	Article 10(a), Well-established use
Active Substance	Methadone hydrochloride.
Form	Concentrate for oral solution
Strength	10 mg/ml
MA Holder	INN-FARM d.o.o. Maleševa ulica 014 1000 Ljubljana Slovenia
RMS	UK
CMSs	Austria, Czech Republic, Germany, Hungary, Italy, Poland, Portugal, Romania, Slovak Republic and Spain
Procedure Number	UK/H/5165/001/DC
Timetable	Day 210: 1st August 2013

Module 2
Summary of Product Characteristics

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.

Module 3
Patient Information Leaflet

In accordance with Directive 2010/84/EU the Patient Information Leaflets (PIL) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.

Module 4

Labelling


Batch No:
EXP:
Methadone hydrochloride
10 mg/ml Concentrate for oral solution
MISYO
1000 ml
DISPENSING PACK ONLY
DISPENSING PACK ONLY
1000 ml
MISYO
10 mg/ml
Concentrate for oral solution
Methadone hydrochloride
Concentrate for oral solution
POM
CD
InnFarm
Each 1 ml of the concentrate for oral solution contains 10 mg of methadone hydrochloride.
Also contains: sorbitol (E420).
See leaflet for further information.
For oral use.
Read the package leaflet before use.
Use as directed by the doctor.
This pack size should be used by healthcare professionals only.
This product is intended to be diluted with water, purified.
Keep out of the reach and sight of children.
Store below 25°C in the original package to protect from light.
After first opening store below 25°C in the original package to protect from light, for not more than 90 days.
Once diluted to concentration of 1 mg/ml or 5 mg/ml it has a 14 days shelf-life when stored in PET bottles below 25°C protected from light.
PL 40168/0001
Marketing Authorisation Holder:
INN-FARM d.o.o.
Maleševa ulica 014,
1000 Ljubljana, Slovenia
DISPENSING PACK ONLY
1000 ml
MISYO
10 mg/ml
Concentrate for oral solution
Methadone hydrochloride
Concentrate for oral solution
InnFarm


DISPENSING PACK ONLY
1000 ml
MISYO
10 mg/ml Concentrate for oral solution
Methadone hydrochloride
Each 1 ml of the concentrate for oral solution contains 10 mg of methadone hydrochloride.
Also contains: sorbitol (E420).
See leaflet for further information.
For oral use.
Read the package leaflet before use.
Use as directed by the doctor.
This pack size should be used by healthcare professionals only.
This product is intended to be diluted with water, purified.
Keep out of the reach and sight of children.
Store below 25°C in the original package to protect from light.
After first opening store below 25°C in the original package to protect from light, for not more than 90 days.
Once diluted to concentration of 1 mg/ml or 5 mg/ml it has a 14 days shelf-life when stored in PET bottles below 25°C protected from light.
PL 40168/0001
Concentrate for oral solution
POM
CD
InnFarm

Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMSs) considered that the application for Misyo 10 mg/ml concentrate for oral solution for substitution therapy for maintenance of opioid dependence in adults in conjunction with appropriate medical, social and psychosocial care could be approved.

This application was submitted under article 10a, well-established use (bibliographic) application, of Directive 2001/83/EC (as amended).

With UK as the RMS in this Decentralised Procedure (UK/H/5165/001/DC), INN-FARM d.o.o. applied for the Marketing Authorisation for Misyo 10 mg/ml concentrate for oral solution in Austria, Czech Republic, Germany, Hungary, Italy, Poland, Portugal, Romania, Slovak Republic and Spain.

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.

No new non-clinical or clinical studies were necessary for this application, which is acceptable given that this is a bibliographic application for a product containing an active ingredient of a well-established use.

The RMS has been assured that acceptable standards of GMP are in place for this product type at all sites responsible for the manufacture and assembly of this product.
For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS considers that the Pharmacovigilance System as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. A detailed Risk Management Plan has been provided. This is satisfactory.

All member states agreed to grant a Marketing Authorisation for the above product at the end of the procedure (Day 210 – 1st August 2013). After a subsequent national phase, the UK granted a Marketing Authorisation for this product on 19th August 2013 (PL 40168/0001).

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Misyo 10 mg/ml concentrate for oral solution
Name(s) of the active substance(s) (USAN)	Methadone hydrochloride
Pharmacotherapeutic classification (ATC code)	Drug used in opioid dependence ATC code: N07BC02
Pharmaceutical form and strength(s)	Concentrate for oral solution
Reference numbers for the Decentralised Procedure	UK/H/5165/001/DC
Reference Member State	United Kingdom
Concerned Member States	Austria, Czech Republic, Germany, Hungary, Italy, Poland, Portugal, Romania, Slovak Republic and Spain.
Marketing Authorisation Number(s)	PL 40168/0001
Name and address of the authorisation holder	INN-FARM d.o.o. Maleševa ulica 014 1000 Ljubljana Slovenia

III SCIENTIFIC OVERVIEW AND DISCUSSION

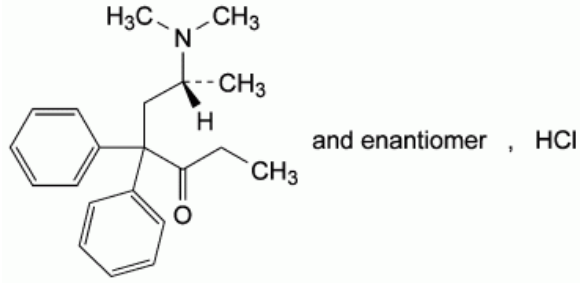
III.1 QUALITY ASPECTS

DRUG SUBSTANCE

INN: Methadone hydrochloride

Chemical Names: (6*RS*)-6-(Dimethylamino)-4, 4-diphenylheptan-3-one hydrochloride
1,1-Diphenyl-1-(2-dimethylaminopropyl)-2-butanone hydrochloride

Structure:



Molecular formula: $C_{21}H_{28}ClNO$

Molecular weight: 345.9 g/mol

Physical form: White to almost white, crystalline powder.

Solubility: The substance is soluble in water and freely soluble in ethanol (96 per cent).

Methadone hydrochloride is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance methadone hydrochloride are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

DRUG PRODUCT

Other Ingredients

Other ingredients consist of the pharmaceutical excipients sorbitol, liquid non-crystallising (E420), glycerol (E422), sodium benzoate (E211), citric acid monohydrate (E330), colour brilliant blue FCF (E133) and water purified. A rationale for the inclusion of each excipient is provided.

All excipients, except the colouring agent brilliant blue FCF (E133), comply with EEC requirements. Satisfactory Certificates of Analysis have been provided for these excipients.

The above excipients do not contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of this product.

Pharmaceutical Development`

Suitable pharmaceutical development data have been provided for this application.

Manufacture

Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on commercial

batches have been provided. The results are satisfactory.

Finished Product Specifications
The finished product specification is satisfactory. Test methods have been described and adequately validated. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Container Closure System
The finished product is supplied in type III, brown glass bottle sealed with screw cap polypropylene (PP) 28 with polyethylene (PE)-liner or with screw cap PP 28 child-resistant tamper evident ring with embossing and PE-liner, and a package leaflet in a carton box. The pack sizes are 100 ml and 1000 ml.

Specifications and Certificates of Analysis for the primary packaging material have been provided. These are satisfactory. All primary packaging is controlled to European Pharmacopoeia standards and complies with relevant guidelines.

Stability
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, shelf-lives of 24 months for unopened bottles, 90 days after opening and 14 days after dilution have been set. The proposed storage conditions are “Store below 25°C in the original package to protect from light” for unopened bottles and after first opening “store below 25°C in the original package to protect from light, for not more than 90 days”.

Once diluted to concentration of 1 mg/ml or 5 mg/ml it has a 14 days shelf-life when stored in polyethylene terephthalate (PET) bottles below 25°C protected from light.

These are satisfactory.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SmPC, PIL and labelling are pharmaceutically satisfactory.

A package leaflet has been submitted to the MHRA together with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

The Marketing Authorisation Holder has committed to submit mock-ups for any non-marketed pack size to the relevant regulatory authorities for approval before those packs are marketed.

Marketing Authorisation Application (MAA) Form
The MAA form is pharmaceutically satisfactory.

Expert Report/Quality Overall Summary
A quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
There are no objections to the approval of this product from a pharmaceutical point of view.

III.2 NON-CLINICAL ASPECTS
PHARMACODYNAMICS, PHARMACOKINETICS, TOXICOLOGY
The pharmacodynamic, pharmacokinetic and toxicological properties of methadone hydrochloride are well-known. Thus, the applicant has not provided additional studies and further studies are not required. An overview based on a literature review is, thus, appropriate.

A non-clinical overview has been provided, written by an appropriately qualified person. This is satisfactory.

Suitable justification has been provided for non-submission of an environmental risk assessment.

There are no objections to the approval of this product from a non-clinical point of view.

III.3 CLINICAL ASPECTS
CLINICAL PHARMACOLOGY
Clinical Pharmacology and Efficacy
This application was submitted as an abridged application according to Article 10a of Directive 2001/83/EC, as amended, a well-established use application.

No new clinical studies were conducted, which is acceptable given that this is a well-established use application containing an active substance that has been in clinical use for many years.

Safety
No new safety concerns have been raised by this application.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling
The SmPC, PIL and labelling are medically satisfactory.

Clinical Expert Report
The clinical expert report is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Marketing Authorisation Application (MAA) Form
The MAA form is medically satisfactory.

Clinical Conclusion
There are no objections to the approval of this product from a clinical point of view.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Misyo 10 mg/ml concentrate for oral solution are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL

No new non-clinical data were submitted and none are required for applications of this type.

CLINICAL

No new efficacy data were submitted and none are required for applications of this type. As the safety profile of methadone hydrochloride is well-known, no additional data were required. No new or unexpected safety concerns arose from this application.

PRODUCT LITERATURE

The SmPC, PIL and labelling are satisfactory and consistent with those for similar marketed products.

RISK-BENEFIT ASSESSMENT

The quality of the product is acceptable and no new non-clinical or clinical concerns have been identified. Extensive clinical experience with methadone hydrochloride is considered to have demonstrated the therapeutic value of the compound. The risk-benefit assessment is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome