Decentralised Procedure

Public Assessment Report

L-Methadone Molteni 5 mg/ml oral solution
Levomethadone hydrochloride

DE/H/3805/001/DC

Applicant:
L. Molteni & C. dei F.lli Alitti Società di Esercizio SpA

Reference Member State	DE

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ADMINISTRATIVE INFORMATION

Proposed name of the medicinal product in the RMS	L-Methadone Molteni 5 mg/ml Lösung zum Einnehmen
Name of the drug substance (INN name):	Levomethadonhydrochlorid
Pharmaco-therapeutic group (ATC Code):	N07BC05
Pharmaceutical form(s) and strength(s):	Oral solution 5 mg/ml
Reference Number(s) for the Decentralised Procedure	DE/H/3805/001/DC
Reference Member State:	DE
Concerned Member States:	ES, IT, PL FR and UK withdrawn
Applicant (name and address)	L. Molteni & C. Dei F.lli Alitti Società di Esercizio S.p.A. Strada Statale 67, Fraz. Granatieri 50018 Scandicci (Firenze), Italy

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the application for *L-Methadone Molteni 5 mg/ml Lösung zum Einnehmen*, is indicated for use in the "Substitution therapy for maintenance of opioid dependence in adults in conjunction with appropriate medical, social and psychosocial care" is approved.

II. EXECUTIVE SUMMARY

II.1 Problem statement

For generic application this section is not applicable.

II.2 About the product

L-Methadone Molteni 5 mg/ml Lösung zum Einnehmen is an oral solution, containing levomethadone hydrochloride as active substance. Levomethadone is the active enantiomer of methadone. It has a 10-fold higher affinity at μ and δ receptors than d-methadone; it prevents the occurrence of opioid withdrawal symptoms, while d-methadone is ineffective (Scherbaum et al., 1996; Isbel et al., 1948). The originator product L-Polamidon® was registered as drop formulation and solution for injection in Germany in 1963 and marketed since 1965 as an analgesic for severe pain. An oral solution was approved and introduced in 2001 indicated for substitution therapy in opioid addicted subjects. Levomethadone reduces withdrawal symptoms in people addicted to heroin or other narcotic drugs without causing the "high" associated with the drug addiction. Levomethadone treatment is an integral part of detoxification and maintenance programs in case of opioid addiction.

II.3 General comments on the submitted dossier

This decentralised application concerns a generic version of levomethadone hydrochloride, under the trade name *L-Methadone Molteni 5 mg/ml Lösung zum Einnehmen*. In this Assessment Report the name *L-Methadone Molteni 5mg/ml* is used.

The data for this application are presented in accordance with Article 10(1) of Directive 2001/83/EC (generic application). The originator product, L-Polamidon® Lösung zur Substitution by Sanofi-Aventis Deutschland GmbH, was approved in Germany in January 2001.

The applicant, L. Molteni & C. Dei F.lli Alitti Società di Esercizio S.p.A., Italy, applies through the Decentralised Procedure with Germany acting as reference member state (RMS) and ES, FR, IT, PL, UK as concerned member states (CMS). However, the applicant decided to withdraw the application in FR and UK.

II.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles.

The RMS has been assured that acceptable standards of GMP are in place for these product types 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.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance

The active substance Levomethadone hydrochloride is described in the European Pharmacopoeia (Ph. Eur.). The quality of the drug substance Levomethadone hydrochloride is controlled in compliance with the corresponding monograph of the European Pharmacopoeia (Ph. Eur.).

Drug Product
The data provided gave the assurance of the quality of the drug product. The ingredients and the manufacturing process of the drug product are considered suitable to produce a pharmaceutical product of the proposed quality. All relevant quality characteristics of the drug substance and the drug product (release and shelf-life) are specified and all proposed limits are accepted. The description of the analytical methods used to analyse the drug substance and drug product are adequate, the validation results are plausible. Covering pilot scale batches stability has been shown over a period of 24 months. A shelf-life of 36 months has been supported by 24 months data from pilot batches and by 34 months data from lab scale batches.

III.2 Non clinical aspects

Pharmacology, Pharmacokinetics, Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of levomethadone are well known. As levomethadone is a widely used, well-known active substance, the applicant has not provided additional non-clinical studies and further non-clinical studies are not required. Overview based on literature review is, thus, appropriate. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

Environmental Risk Assessment (ERA)
Since the medicinal product is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.3 Clinical aspects

Pharmacokinetics
According to the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr, 20 January 2010), "if the test product is an aqueous oral solution at time of administration and contains an active substance in the same concentration as an approved oral solution, bioequivalence studies may be waived". The proposed medicinal product falls into this category.
The Applicant for the proposed medicinal product seeks a waiver for conducting in vivo bioequivalence studies comparing its product with the reference medicinal product based on the current EU legislation cited above.
The proposed formulation is an aqueous oral solution and contains Levomethadone hydrochloride at the same concentration as the already EU approved oral solution / reference product (Polamidon® Lösung zur Substitution, oral solution, by Sanofi-Aventis Deutschland GmbH).
Moreover, in the proposed formulation, there are no excipients which may affect gastrointestinal transit (e.g. sorbitol, mannitol, etc.), absorption (e.g. surfactants or excipients that may affect transport proteins), in vivo solubility (e.g. co-solvents) or in vivo stability of the active substance. Justification for a biowaiver is therefore acceptable.

Pharmacodynamics
N/A

Clinical efficacy
N/A

Clinical safety
N/A

User Testing
The applicant has provided a Package Leaflet User Testing Report dated 27-02-14 (Project Number: 0114/MOL/07). The results demonstrated that at least 90% of the participants were able to find each point of information. It also showed that at least 90% of those participants were able to understand the information. The leaflet therefore fulfils the EU requirements for User Testing.

Pharmacovigilance system (DDPS)
The Applicant/Proposed Future MAH has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

Risk Management Plan
The MAH presented the following summary of safety concerns:

Summary of safety concerns	
Important identified risks	• Respiratory depression • QT prolongation and cardiac arrhythmias) • Fatal overdose • Use during pregnancy and lactation • Misuse and/or abuse • Dependence • Drug withdrawal syndrome • CNS depression • Off label use • Risk of paediatric accidental intoxication
Important potential risks	Risk of medication errors
Important missing information	None

Educational material as an additional measure helpful to prevent medication errors will be submitted to the CMS IT for approval after finalisation of the procedure but prior marketing of the product.

Periodic Safety Update Report (PSUR)
PSUR cycle with re-evaluation of the effectiveness of the risk management measures will be shortened to a 1-year frequency for the first four years from the actual start of marketing of the product, then every 3 years till the DLP foreseen in the EURD list for levomethadone (2025).

IV. BENEFIT RISK ASSESSMENT
The originator product L-Polamidon® was registered as drop formulation and solution for injection in Germany in 1963 and marketed since 1965 as an analgesic for severe pain. An oral solution was approved and introduced in 2001 indicated for substitution therapy in opioid addicted subjects. This decentralised application concerns a generic version of levomethadone hydrochloride, under the trade name L-Methadone Molteni 5 mg/ml Lösung zum Einnehmen. The proposed formulation is an aqueous oral solution and contains Levomethadone hydrochloride at the same concentration as the originator product. Justification for waiving bioequivalence studies is acceptable. The benefit-risk-balance is considered to be positive.
The application is approved.
For intermediate amendments see current product information.