COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Maddoflox 500 mg film-coated tablets (levofloxacin hemihydrate)

NL License RVG: 126738

Date: 19 August 2024

This module reflects the scientific discussion for the approval of Maddoflox 500 mg film-coated tablets. The procedure was finalised on 29 November 2022. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
BCS	Biopharmaceutics Classification System
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

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 Maddoflox 500 mg film-coated tablets, from Maddox Pharma Swiss B.V.

The product is an antibacterial agent of the wide spectrum fluoroquinolone group. It is indicated for treatment of the following infections in adults (see sections 4.4 and 5.1):

- Acute bacterial sinusitis
- Exacerbated chronic bronchitis
- Community-acquired pneumonia
- Complicated skin and soft tissue infections

The product should be used for the abovementioned infections only when the use of the usually recommended in these cases antibacterial products is considered inappropriate.

- Complicated infections of the urinary tract and pyelonephritis
- Chronic bacterial prostatitis
- Uncomplicated cystitis (see section 4.4)
- Inhalation anthrax: prevention upon exposure and treatment (see section 4.4)

The product may be used for completion of treatment in patients who have shown improvement upon initial administration of intravenous levofloxacin.

When prescribing the product, the formal recommendations for appropriate administration of antibacterial medicines should be considered.

A comprehensive description of the indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this national procedure, essential similarity is proven between the new product and the innovator product Tavanic 500 mg film-coated tablet, which has been registered in the Netherlands via national procedure (RVG 21812) by Sanofi-Aventis Netherlands B.V. since 9 December 1997.

II. QUALITY ASPECTS

II.1 Introduction

Maddoflox 500 mg is a round, biconvex, and orange film-coated tablet.

Each tablet contains as active substance 500 mg of levofloxacin as levofloxacin hemihydrate.

The excipients are:
Tablet-core: crospovidone (E1202), hypromellose (E464), silicified microcrystalline cellulose, anhydrous colloidal silica (E551), microcrystalline cellulose (E460), and sodium stearyl fumarate.
Film-coating: talc (E553b), titanium dioxide (E171), macrogol 4000, polyvinyl alcohol (E1203), sunset yellow (E110), tartrazine (E 102), and soy lecithin (E322).

The film-coated tablets are packed in polyvinyl chloride/polyvinylidene chloride/aluminium (PVC/PVdC/Al) blisters, in carton boxes.

II.2 Drug Substance

The active substance is levofloxacin hemihydrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a light yellowish-white or light yellow crystalline powder and is sparingly soluble in water. It has one chiral centre. Levofloxacin is the S-enantiomer of ofloxacin. It exists in different polymorphic forms, with the hemihydrate form being the relevant form for this product.

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 consists of six steps. In the first step, four starting materials are used. In the final step of the synthesis, two solvents are used. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised and the manufacturing process is described in sufficient detail.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for two full scale batches.

Stability of drug substance
Stability data on the active substance has been provided for three batches in accordance with applicable European guidelines demonstrating the stability of the active substance for 6 months. Based on the data submitted, a retest period could be granted of 24 months when stored under the stated conditions.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

A BCS class 1 biowaiver has been requested. The QC dissolution method has been sufficiently justified.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three full scale batches in accordance with the relevant European guidelines. The tablets are manufactured by wet granulation. The product is manufactured using conventional manufacturing techniques.

Control of excipients

The excipients comply with Ph.Eur. requirements. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identification, identification of colourants, average weight, dissolution, assay, uniformity of dosage, related substances and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. It was demonstrated that levels of impurity B in the finished product at accelerated conditions 40°C/75 %RH for 6 months were below the limit of detection. Considering that risk of the formation of impurity B is very low, the risk of the formation of the nitrosamine as a consequence is therefore also negligible. No further risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data three full scaled batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product has been provided for three full scaled batches stored at 25°C/60%RH with one batch for 36 months and two batches for 24 months. Three batches were stored at 40°C/75%RH for 6 months.in accordance with applicable European guidelines. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. On basis of the data submitted, a shelf life was granted of three years. No specific storage conditions needed to be included in the SmPC or on the label.

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 Maddoflox has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Maddoflox 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.2 Discussion on the non-clinical aspects

This product is a generic formulation of Tavanic which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. 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

Levofloxacin hemihydrate is a well-known active substance with established efficacy and tolerability A clinical overview has been provided, which is based on scientific literature. The MEB agreed that no further clinical studies are required.

For this generic application, no *in vivo* bioequivalence studies were performed. A BCS class I biowaiver has been requested.

IV.2 Pharmacokinetics

Biowaiver

According to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**) *in vivo* bioequivalence studies may be exempted if an assumption of equivalence in *in vivo* performance can be justified by satisfactory *in vitro* data. For this product, a BCS-based biowaiver is applicable for immediate release, through the waiver approach for solid pharmaceutical products for oral administration with systemic action having the same pharmaceutical form. The waiver can be accepted when the following characteristics are demonstrated with *in vitro* studies:

- The drug should not have a narrow therapeutic index
- The drug substance has high solubility and complete absorption (BCS class I)
- The test and reference product have either very rapid (>85 % within 15 min) or similarly rapid (85% within 30 min) *in vitro* dissolution characteristics
- Excipients that might affect bioavailability are qualitatively and quantitatively the same. In general, the use of the same excipients in similar amounts is preferred

The characteristics described in the biowaiver were assessed. Based on the submitted information and *in vitro* data, it has been demonstrated that levofloxacin hemihydrate (drug substance) cannot be considered as a drug with narrow therapeutic index. The classification BCS class I was confirmed due to the demonstrated high solubility and complete absorption of the drug substance. The test and reference products show very rapid (>85 % within 15 min) *in vitro* dissolution. Furthermore, the excipients used in the test and reference products are the same and they are used in usual amounts. Based on the results, the waiver is accepted.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, 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 Maddoflox.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

The MEB agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Tavanic. No new clinical studies were conducted. Risk management is adequately addressed. A BCS class I biowaiver has been granted. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) 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 language used for the purpose of user testing the PL was Dutch.

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Levofloxacine Beximco 250 mg and 500 mg, film-coated tablets (NL/H/3238/001-2). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Maddoflox 500 mg film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Tavanic 500 mg film-coated tablets. Tavanic is a well-known medicinal product with an established favourable efficacy and safety profile.

A BCS class I biowaiver has been granted.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated for Maddoflox with the reference product, and have therefore granted a marketing authorisation. The national procedure was finalised with a positive outcome on 29 November 2022.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
Type IAin: B.II.b.2.c.1	*Change to importer, batch release arrangements and quality control testing of the finished product.* • *Replacement or addition of a manufacturer responsible for importation and/or batch release.* ○ *Not including batch control/testing.*	Yes	16-01-2023	Approved	
Type IB: C.I.2.a	*Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/biosimilar medicinal products following assessment of the same change for the reference product.* • *Implementation of change(s) for which no new additional data are submitted by the MAH.*	Yes	28-11-2023	Approved	
Art.61(3)	*To add English translations of PIL and labelling to the product information of the above product in order to have bilingual packaging texts*	Yes	29-03-2023	Approved	
Type IB: C.I.11.z	*Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the risk management plan* • *Other variation*	No	08-07-2024	Approved	