CMDh/223/2005
February 2014

Public Assessment Report

Scientific discussion

Neumax 750 mg film-coated tablets (levofloxacin)

ES/H/0916/001/DC

Date: 09 April 2025

This module reflects the scientific discussion for the approval of Neumax 750 mg film-coated tablets. The procedure was finalised at 10 September 2024. For information on changes after this date please refer to the module ôUpdateô.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Neumax 750 mg film-coated tablets, from Laboratorios Gebro Pharma S.A.

The product is indicated for the treatment of community-acquired pneumonia (CAP) in adults.

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

The marketing authorisation has been granted pursuant to Article 10.3 of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Film-coated tablets, containing 750 mg of levofloxacin hemihydrate. The container closure system of the product consists of PVC/Aluminium blisters.

II.2 2.2Drug Substance

Neumax 750 mg film-coated tablets contains as active substance Levofloxacin hemihydrate which is described in the Ph. Eur. 2598. In addition, a Certificate of Suitability has been granted by EDQM to the selected manufacturer.

The INN is Levofloxacin hemihydrate; It is the (-)-S-isomer of ofloxacin. Levofloxacin can potentially exist in different hydrate (polymorphic) forms; the hemihydrate form is used.

The specifications are in accordance with Ph.Eur. requirements. The re-test period granted in the CEP is 60 months

II.3 Medicinal Product

The pharmaceutical development has been supported on the basis of the similarity between the reference product (Tavanic) and the proposed formulation for Neumax 750 mg film-coated tablets.

The manufacturing site of the drug product and its responsibilities are disclosed. A commercial batch size is proposed is validated and the corresponding batch formula is presented. The manufacturing process of Levofloxacin 750 mg film-coated tablets has been described. A standard manufacturing process is used which consists of mixing, granulation, drying, sieving, mixing, lubrication, compression, film coating and packaging.

Excipients are controlled according to the corresponding Ph. Eur. monographs, except for non-compendial excipients.

The finished product specifications cover appropriate parameters described in Ph. Eur. for this pharmaceutical form and the acceptance limits proposed are generally acceptable.

Analytical methods are described and validated according to ICH guidelines.

The container closure system of the product consists of PVC/Aluminium blisters. A suitable description of the proposed container closure system is provided. PVC film meets Ph. Eur. requirements and EU legislation for foodstuff. Regarding aluminium foil, a statement of compliance with EU foodstuff regulations has been provided.

The applicant is proposing a shelf-life of 18 months, applying the storage conditions ñDo not store above 30ºC. Store in the original package in order to protect from lightò.

II.4 Discussion on chemical, pharmaceutical and biological aspects

III. NON-CLINICAL ASPECTS

III.1 Critical evaluation of the Non-Clinical Overview

Pharmacodynamic, pharmacokinetic and toxicological properties of levofloxacin are well known. As levofloxacin is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

III.2 Environmental Risk Assessment (ERA)

The Applicant has submitted an ERA based on publicly available data, which not fulfill with the some relevant aspects required for compliance the current guidelines. Therefore, a final conclusion on potential risk of levofloxacin to the environment cannot be drawn until a new updated ERA post-marketing is submitted. In this regard, the Applicant has provided a written commitment to perform a Phase I and Phase II ERA post-marketing for the active ingredient levofloxacin, including an experimentally determined log Kow study and following a tailored testing strategy due to its antibacterial mechanism of action, respectively.

IV. CLINICAL ASPECTS

IV.1 Introduction

For this hybrid application of a film coated tablet the MAH has not submitted any clinical study report. Instead, the Applicant states that a bioequivalence study would not be required for this product and a BCS based biowaiver could be applied.

IV.2 Pharmacokinetics

Biowaiver

The Applicant did not conduct a bioequivalence study and asked for a national Scientific Advice in ES in November 2020 to discuss the possibility of performing a BCS based biowaiver. The applicant provided the following rationale:

Published data suggest that levofloxacin can be classified as a BCS Class I drug substance (high solubility, high permeability). This classification is confirmed by the WHO Prequalification team assignment of BCS Class I to levofloxacin (WHO, 2014), and also by the conclusions reached in three other publications (Frick et al., 1998; Koeppe et al., 2011; Klosinska-Szmurlo et al., 2014).

Here, a biowaiver is applicable as the drug substance in test and reference products are identical (levofloxacin hemyhidrate)

Solubility

Regarding solubility, the applicant has conducted **solubility studies** in four dissolution media (pH 1.2, pH 4.5 acetate buffer, pH 6.8 phosphate buffer, pH 5.5 phosphate buffer) at 37ºC showing that levofloxacin hemihydrate is highly soluble in all the tested dissolution media.

According to the ICH M9 Guideline on biopharmaceutics classification system-based biowaivers (EMA/CHMP/ICH/493213/2018, 2020), a drug substance is considered highly soluble when the highest strength is soluble in 250 mL or less aqueous media within the range of pH 1-6.8 at 37ºC. The highest single estimated administration dose of levofloxacin (750 mg) in 250 mL corresponds to a concentration of 3.0 mg/mL, showing high solubility at the different pH evaluated. Hence, according to the BCS (Biopharmaceutical Classification System) levofloxacin hemihydrate is a highly soluble drug.

Permeability

Regarding **complete absorption**, an open-label, randomised clinical study with a 3-way crossover design, conducted in 23 healthy male volunteers, showed that levofloxacin is rapidly and completely absorbed from 500 mg orally administered tablets with a bioavailability of Ó 99% (Chien et al., 1997). This information is reflected as well in the harmonised SmPC of the RMP, which states that administered levofloxacin is rapidly and almost completely absorbed with peak plasma concentrations being obtained within 1-2 hours. The absolute bioavailability is 99-100% (Tavanic - SmPC [IE], 2021; Tavanic - SmPC [ES], 2022).

The **permeability** of levofloxacin was also studied using the human colorectal carcinoma cell line CaCo-2, resulting in demonstration of high permeability (27.0x10-6 cm/s) and passive transport. The determined permeability data was confirmed by absorption data obtained by means of numerical deconvolution of plasma concentrations (Koeppe et al., 2011).

Composition and excipients

According to the mentioned ICH M9, to qualify for a BCS-based biowaiver, qualitative and quantitative differences in excipients are permitted, except for excipients that may affect absorption, which should be qualitatively the same and quantitatively similar, i.e., within ±10% of the amount of excipient in the reference product. As shown in Table 2.5-2 (comparison between Tavanic 500 mg and the proposed product), none of the excipients that diverge between the two formulations are known to affect gastrointestinal transit, absorption, in vivo solubility or in vivo stability of the active substance (Metry et al., 2022).

Table 2.5-2. Composition of excipients of Levofloxacin 750 mg film-coated tablets versus the RMP

Levofloxacin 750 mg film-coated tablets	Tavanic 500 mg
CORE TABLETS	
Microcrystalline cellulose	Microcrystalline cellulose
Povidone	
Crospovidone	Crospovidone
Silica, colloidal anhydrous	
Sodium stearyl fumarate	Sodium stearyl fumarate
	Hypromellose
COATING TABLETS	
Opadry 03F280010:	
Titanium dioxide	Titanium dioxide
Talc	Talc
Macrogol 6000	Macrogol
Iron oxide	Iron oxide
Hypromellose	Hypromellose

In vitro dissolution

To support the BCS-based biowaiver approach, comparative in vitro dissolution profiles were conducted according to current guidelines. The study protocol (no. 4391-02) as well as the study report (no. 4400-01.PPQ) are enclosed.

The in vitro tests performed by the Applicant show that the dissolution profiles of Levofloxacin 750 mg film-coated tablets and the European RMPs (500 mg and 250 mg separately) are very similar at all pH tested, with a very rapid dissolution characteristics (> 85% in 15 minutes).

Also, as supportive material, the applicant has performed comparative dissolution profiles between the proposed product 750 mg (see above dissolution profiles section) and the US reference product which are also similar at all tested pH, showing > 85% dissolved in 15 minutes.

In the Scientific Advice held in November 2020, the AEMPS agreed that the intended approach of exemption of bioequivalence studies and the justification based on a BCS biowaiver was questionable because BCS biowaivers are designed only for comparisons of the same strength in test and reference products, although deviations are possible if scientifically justified (in this case levofloxacin 750 mg is no longer commercially available in the EU, therefore, the comparison with the reference 250 mg and 500 mg strengths available in the market, is acceptable).

Conclusion on Biowavier:

The justification for BCS (Biopharmaceutics Classification System) - based biowaiver can be accepted.

IV.3 Pharmacodynamics

No new studies on pharmacodynamics have been submitted, which is acceptable for this hybrid application.

IV.4 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 Neumax 750 mg film-coated tablets (levofloxacin).

There are neither proposed additional pharmacovigilance activities nor proposed additional risk minimisation measures planned for Neumax 750 mg film-coated tablets (levofloxacin).

IV.5 Discussion on the clinical aspects

The efficacy and safety of the active substance levofloxacin are established and documented for the reference product.
The MAH demonstrated through a BCS based biowaiver that the in vitro behaviour of the product is similar to the reference product.

V. USER CONSULTATION

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 language used for the purpose of user testing the PIL was english
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.
The test consisted of: a pilot test with 3 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the hybrid product Neumax 750 mg film-coated tablets is found adequate. There are no objections to the approval of Neumax 750 mg film-coated tablets from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated in vitro. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.