CMDh/223/2005
February 2014

Public Assessment Report

Scientific discussion

Levalox 250 mg and 500 mg film-coated tablets
Levofloxacin

HR/H/0100/001-002/DC

Date: 20.03.2015

This module reflects the scientific discussion for the approval of Levalox 250 mg and 500 mg film-coated tablets. The procedure was finalised at January 27th 2015 (day 197). For information on changes after this date please refer to the module 'Update'.

This report includes a summary, on pages 7-9.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Levalox 250 mg and 500 mg film-coated tablets, from Krka Farma d.o.o.

The product is indicated for:
• Acute bacterial sinusitis
• Acute exacerbations of chronic bronchitis
• Community-acquired pneumonia
• Complicated skin and soft tissue infections
For the above-mentioned infections levofloxacin should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of these infections.
• Pyelonephritis and complicated urinary tract infections
• Chronic bacterial prostatitis
• Uncomplicated cystitis
• Inhalation Anthrax: postexposure prophylaxis and curative treatment

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 with Tavanic (250 mg and 500 mg film-coated tablets), Sanofi-Aventis, as the reference product. The reference product Tavanic (250 mg and 500 mg film-coated tablets) has been authorised in UK since June 6, 1997.

The concerned member states (CMS) involved in the procedure were Austria, Bulgaria, Czech Republic, Estonia, Finland, France, Hungary, Ireland, Latvia, Lithuania, Poland, Portugal, Romania, Slovakia, Slovenia, Spain and Sweden.

II. QUALITY ASPECTS

II.1 Introduction

Levalox 250 mg film-coated tablets are pink, oblong, biconvex tablets with a scoreline and dimension 13.7 mm x 6.7 mm and thickness 3.8 mm. Levalox 500 mg film-coated tablets are orange, oblong, biconvex, tablets with a scoreline and dimensions 19.3 mm x 7.8 mm and thickness 5.0 mm. The tablets can be divided into equal doses.

The film-coated tablets are packed in PVC/PE/PVDC - Alu foil blisters.

The excipients are:
Tablet core - microcrystalline cellulose, hydroxypropylcellulose, crospovidone (type A), magnesium stearate
Film coating - hypromellose, macrogol 4000, indigo carmine (E132), sunset yellow FCF (E110), titanium dioxide (E171), iron red oxide (E172), iron yellow oxide (E172) (only for 500 mg).

II.2 Drug Substance

Levofloxacin hemihydrate is not described in current Ph.Eur.

Levofloxacin hemihydrate is almost white to light yellow crystalline powder which is soluble in methylene chloride and acetic acid and sparingly soluble in water. The structure of levofloxacin hemihydrate has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on hydrate forms and chirality is presented. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

Active substance specification is acceptable for batch control of levofloxacin hemihydrate which is used in oral and parenteral preparations. All submitted methods are sufficiently described and validated. Data for the container closure system are considered adequate and quality/stability of active substance in proposed primary packaging has been confirmed.

II.3 Medicinal Product

The development of the formulation has been clearly described. Qualitative and quantitative composition of active substance in test product is identical with referent product whereas excipients are not identical, but are similar. Development of the dissolution method has been sufficiently described.
The manufacture of the product is considered as a common standard process. The manufacturing processes and in process control testing have been described in sufficient details. Acceptable validation data have been provided. The suitability of the excipients has been proved. None of the excipients is of human or animal origin and does not present a TSE/BSE risk.
The product specifications cover appropriate parameters for this dosage form and are considered acceptable. Analytical methods of all parameters listed in the specifications have been sufficiently described and validated in line with ICH guidance. The provided characterisation of potential impurities is acceptable.
The presented primary packaging system for tablets, transparent PVC/PE/PVDC Aluminium foil blister is standard packaging system for oral solid formulations. The provided specifications and information for the proposed container closure system are considered as sufficient for the intended use and maintains quality and stability of the product for the entire shelf life.
Based on provided data, a shelf life of 60 months without any specific storage conditions is acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Levalox film-coated tablets have 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 Levalox 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.

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.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Bioequivalence studies

The study was single center, randomized, single dose, laboratory-blinded, 2-period, 2-sequence, crossover, comparative bioavailability study between Levalox 500 mg film coated tablets and the innovator product Tavanic 500 mg film coated tablets. The study was performed in 24 healthy male and female volunteers under fasting conditions with a wash out period of 7 days between two administrations. Safety was also monitored during the study. This study was conducted in accordance with requirements of the current bioequivalence Guideline (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr**; London 2010) and thus, should as such be considered as the pivotal bioequivalence study for this application. As a part of the bioequivalence study, validation of bioanalytical method was performed according to current Guideline on bioanalytical method validation EMEA/CHMP/EWP/192217/2009.

Conclusion on bioequivalence studies:

Based on the submitted bioequivalence study Levalox is considered bioequivalent with Tavanic.

IV.2 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 Levalox.

- Summary table of safety concerns as approved in RMP

Summary of safety concerns	
Important identified risks	Hypersensitivity, anaphylaxis
	Seizure
	Tendinopathy
	Antibiotic associated diarrhoea (including Clostridium difficile colitis)
	Peripheral neuropathy
	Hepatotoxicity
	Renal failure
	Serious vision disorders
	Serious bullous skin reactions
	Psychotic reactions
	Exacerbation of myasthenia gravis
	Use of levofloxacin in children and growing adolescents
	Prolongation of QTc interval and potentially QTc-prolongation related clinical conditions
Important potential risks	Photosensitivity reactions
	Arthropathy in paediatric patients
Missing information	Pragnancy and breast feeding
	Safety in patients with moderate and severe renal impairment

In line with the RMP of the reference product no additional pharmacovigilance activity is currently warranted.

IV.3 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. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to already approved readability test for Levofloxacin 250 & 500 mg film coated tablets. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Levalox 250 mg and 500 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic form of Tavanic 250 mg and 500 mg film-coated tablets, respectively. Tavanic is a well-known medicinal product with an established favourable efficacy and safety profile.
Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

There was no discussion in the CMD(h). The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated with the reference product and the application was approved. The decentralised procedure was finalized with a positive outcome on 27 January 2015.

CMDh/305/2013
July 2014, Rev.01

Summary Public Assessment Report

Generics

Levalox 250 mg and 500 mg film-coated tablets
Levofloxacin

HR/H/0100/001-002/DC

Date: 20.03.2015

Summary Public Assessment Report

Generics

Levalox

Levofloxacin, film-coated tablets, 250 mg
Levofloxacin, film-coated tablets, 500 mg

This is a summary of the public assessment report (PAR) for Levalox. It explains how Levalox was assessed and its authorisation recommended as well as its conditions of use. It is not intended to provide practical advice on how to use Levalox.

For practical information about using Levalox, patients should read the package leaflet or contact their doctor or pharmacist.

What is Levalox and what is it used for?
Levalox is a 'generic medicine'. This means that Levalox is similar to a 'reference medicine' already authorised in the European Union (EU) called Tavanic.
Levalox is used to treat infections of the:
- Sinuses
- Lungs, in people with long-term breathing problems or pneumonia
- Urinary tract, including your kidneys or bladder
- Prostate gland, where you have a long lasting infection
- Skin and underneath the skin, including muscles. This is sometimes called 'soft tissue'

In some special situations, Levalox tablets may be used to lessen the chances of getting a pulmonary disease named anthrax or worsening of the disease after you are exposed to the bacteria causing anthrax.

How does Levalox work?
Levalox tablets contain a medicine called levofloxacin. This belongs to a group of medicines called antibiotics. Levofloxacin is a 'quinolone' antibiotic. It works by killing the bacteria that cause infections in your body.

How is Levalox used?
The pharmaceutical form of Levalox is film-coated tablet and the route of administration is oral.

Please read section 3 of the PL for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

A doctor will decide on how many Levalox tablets should be taken. The dose will depend on the type of infection and the part of the body infected. The length of the treatment will depend on the seriousness of the infection.

A patient should keep out of direct sunlight while taking this medicine and for 2 days after the end of treatment.

The medicine can only be obtained with a prescription.

What benefits of Levalox have been shown in studies?
Because Levalox is a generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine, Tavanic. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Levalox?
Because Levalox is a generic medicine and is bioequivalent to the reference medicine, its benefits and possible side effects are taken as being the same as the reference medicine.

Why is Levalox approved?
It was concluded that, in accordance with EU requirements, Levalox has been shown to have comparable quality and to be bioequivalent to reference medicine. Therefore, the HALMED decided that, as for reference medicine called Tavanic, the benefits are greater than its risk and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Levalox?
A risk management plan has been developed to ensure that Levalox is used as safely as possible. Based on this plan, safety information has been included in the summary of product characteristics and the package leaflet for Levalox, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously as well.

Other information about Levalox
The marketing authorisation for Levalox was granted on 26 February 2015.

The full PAR for Levalox can be found on the website http://mri.medagencies.org/Human/Product/Details/43335. For more information about treatment with Levalox, read the package leaflet (http://mri.medagencies.org/download/HR_H_0100_001_FinalPI.pdf) or contact your doctor or pharmacist.

This summary was last updated in 03-2015.