COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Erelan 400 mg film-coated tablets

(moxifloxacin hydrochloride)

NL/H/4140/001/DC

Date: 7 March 2019

This module reflects the scientific discussion for the approval of Erelan 400 mg film-coated tablets. The procedure was finalised at 26 September 2018. 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
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
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
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Erelan 400 mg film-coated tablets, from Medochemie Limited.

The product is indicated for: indicated for the treatment of the following bacterial infections in patients of 18 years and older caused by bacteria susceptible to moxifloxacin.

Moxifloxacin should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of these infections or when these have failed:

- Acute bacterial sinusitis (adequately diagnosed).
- Acute exacerbations of chronic bronchitis (adequately diagnosed).
- Community acquired pneumonia, except severe cases.
- Mild to moderate pelvic inflammatory disease (i.e. infections of female upper genital tract, including salpingitis and endometritis), without an associated tubo-ovarian or pelvic abscess.
  Moxifloxacin is not recommended for use in monotherapy of mild to moderate pelvic inflammatory disease but should be given in combination with another appropriate antibacterial agent (e.g. a cephalosporin) due to increasing moxifloxacin resistance of Neisseria gonorrhoeae unless moxifloxacin-resistant Neisseria gonorrhoeae can be excluded.

Moxifloxacin may also be used to complete a course of therapy in patients who have shown improvement during initial treatment with intravenous moxifloxacin for the following indications:

- Community-acquired pneumonia.
- Complicated skin and skin structure infections.

Moxifloxacin should not be used to initiate therapy for any type of skin and skin structure infection or in severe community-acquired pneumonia.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Avelox 400 mg, film-coated tablets (NL License RVG 28118) which has been registered in the Netherlands by Bayer B.V. since 17 October 2002 through mutual recognition procedure DE/H/0155/002.

The concerned member states (CMS) involved in this procedure were Bulgaria, Cyprus, Estonia, Spain, Lithuania, Malta and Romania.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Erelan is a red oval-shaped, biconvex film-coated tablet, embossed with "MC". Each tablet contains 400 mg moxifloxacin (as hydrochloride).

The film-coated tablets are packed in Al/Al blisters.

The excipients are:
Tablet core - microcrystalline cellulose (E460), lactose monohydrate 320 croscarmellose sodium (E468) and magnesium stearate (E470b)
Film-coat - hypromellose (E464), macrogol (E1521), titanium dioxide (E171) and red iron oxide (E172)

II.2 Drug Substance

The active substance is moxifloxacin hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a light yellow or yellow powder or crystals, slightly hygroscpic, and is sparingly soluble in water, slightly soluble in ethanol (96%) and practically insoluble in acetone. The drug substance exhibits polymorphism and the crystalline monohydrate form is used.

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.

<u>Manufacturing process</u>
The manufacturing process consists of six steps followed by a purification step. No metal catalysts are used. The proposed starting materials are acceptable given their route of synthesis. The active substance was sufficiently characterised with regard to chemical structure and polymorphic form. The impurities have been adequately discussed.

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. with additional tests on polymorphic form and residual solvents. Several impurities, that can not be determined with the Ph. Eur. method, are routinely tested with an in-house method. Batch analytical data demonstrating compliance with this specification have been provided for four batches.

Stability of drug substance

Stability data on the active substance have been provided for six batches where three batches were stored at 30°C/65 % RH (up to 60 months) and 40°C /75% RH (6 months). The drug substance was shown to be stable for 60 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. The choice of excipients is justified and their functions explained. The same excipients as in the reference product were selected and development focussed on the optimisation of the composition and the manufacturing conditions. A BCS-based biowaiver is requested, and adequate solubility and dissolution data in accordance with the Guideline on Bioequivalence Testing has been provided in order to support this waiver. The provided dissolution profiles of the test and reference product batches at three different pH values show rapid and complete dissolution (> 85% dissolved in all cases). Overall, the pharmaceutical development is acceptable.

Manufacturing process

The manufacturing process consists of drying, mixing, compression, film-coating, and packing. It is considered to be a standard process. The manufacturing process has been described in sufficient detail and has been validated according to relevant European guidelines. Process validation data on the product have been presented for two commercial scaled batches in accordance with the relevant European guidelines. Process validation for full-scale batches will be performed post authorisation.

Control of excipients

Apart from the iron oxide red all excipients comply with the Ph. Eur. For the iron oxide reference is made to EU Regulation 231/2012. 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 description, identification, average weight, disintegration, water content, uniformity of dosage units, dissolution, related substances, assay, identification of colourants, and microbiological examination. Limits in the specification have been justified and are considered appropriate for adequate quality control

of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from two commercial batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for two commercial batches stored at 25°C/60% RH (12 months), and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The tablets were stored in their commercial packaging. No significant changes or trends were observed in the currently available stability data. Based on the provided stability data, the proposed shelf life of 24 months without any specific storage conditions can be approved.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

The used lactose monohydrate is safe with respect to transmittance of TSE. No other materials of animal or human origin are used in the manufacturing process of the drug substances or of the drug product.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Erelan 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 Erelan 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 Avelox 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 member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Moxifloxacin hydrochloride is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

BCS-Biowaiver

To support the application, the MAH has not submitted an *in vivo* bioequivalence study, but instead request for a BCS-based biowaiver. From a quality perspective, a BCS-class I based biowaiver is acceptable if the solubility of the substance is high and if very rapid or similarly rapid dissolution characteristics of the test and reference products have been demonstrated.

The MAH submitted data to support the full biowaiver for the 400 mg tablets. Erelan 400 mg film-coated tablets were developed as a generic version of Avelox 400 mg, film-coated tablet. Consequently, they contain the same qualitative and quantitative composition in term of active substance (moxifloxacin), at the same concentrations, in the same pharmaceutical dosage form, to be administered by the same administration route, oral.

Moxifloxacin is considered to be a BCS Class I drug and not a narrow therapeutic drug. The test tablet formulation and the reference formulation contain comparable excipients and no excipients which could be considered critical with regard to absorption. Both test and reference formulation dissolves very rapidly at pH 1.2, 4.5 and 6.8. Since all criteria regarding a BCS-based biowaiver are fulfilled, a biowaiver can be granted.

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 Erelan.

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

Important identified risks	Hypersensitivity, anaphylaxis Prolongation of QTc interval Seizure Peripheral neuropathy Tendinopathy Hepatotoxicity Antibiotic associated diarrhoea (including colitis) Renal failure

	Serious vision disorder Serious bullous skin reactions Depression, suicidality and psychosis Serious haematological disorders Exacerbation of myasthenia gravis
Important potential risks	Bradycardia Rhabdomyolysis, myositis and myopathy Muscle rupture Ligament rupture Selection of drug resistant isolates Retinal detachment
Missing information	Use of moxifloxacin in children and growing adolescents Arthropathy (in paediatrics patients)

The member states 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 Avelox. No new clinical studies were conducted. The MAH requested and was granted a BCS-based biowaiver. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

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 the innovator Avelox. 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

Erelan 400 mg film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Avelox 400 mg, film-coated tablets. Avelox is a well-known medicinal product with an established favourable efficacy and safety profile.

Since a BCS-based biowaiver has been granted, no bioequivalence study is deemed necessary.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Erelan with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 26 September 2018.

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