COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Renixola 200 mg, film-coated tablets (sorafenib tosylate)

NL/H/5391/001/DC

Date: 31 January 2022

This module reflects the scientific discussion for the approval of Renixola 200 mg, film-coated tablets. The procedure was finalised on 11 August 2021. 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
QC	Quality Control
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 Renixola 200 mg, film-coated tablets, from Gedeon Richter Plc.

The product is indicated for:

Hepatocellular carcinoma
Renixola is indicated for the treatment of hepatocellular carcinoma (see section 5.1 of the SmPC).

Renal cell carcinoma
Renixola is indicated for the treatment of patients with advanced renal cell carcinoma who have failed prior interferon-alpha or interleukin-2 based therapy or are considered unsuitable for such therapy.

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 Nexavar 200 mg, film-coated tablets which has been registered in the EEA by Bayer AG since July 2006 by the centralised procedure EU/1/06/342.

The concerned member states (CMS) involved in this procedure were Bulgaria, Czech Republic, Hungary and Romania.

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

II. QUALITY ASPECTS

II.1 Introduction

Renixola is a red-brown, round, biconvex film-coated tablet, debossed with “200” on side and plain on the other side and contains as active substance 200 mg of sorafenib (as tosylate).

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

The excipients are:
Tablet core – hypromellose 2910 (E464), croscarmellose sodium (E468), cellulose microcrystalline (E460), magnesium stearate (E470b) and sodium laurilsulfate (E514).

Tablet coating – hypromellose 2910 (E464), titanium dioxide (E171), macrogol 3350 (E1521) and red iron oxide (E172).

II.2 Drug Substance

The active substance is sorafenib tosylate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white to slight yellow crystalline powder. Sorafenib tosylate is very soluble in dimethylformamide and practically insoluble in methanol, acetonitrile or water. The active substance has no asymmetric carbons. It exhibits polymorphism. Crystalline form III is used for the medical 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 of drug substance is described in sufficient detail. Reaction sequences and process flow charts are provided together with a detailed narrative of the manufacturing process. The three proposed starting materials are acceptable.

Results of analysis have been provided of batches starting materials from all suppliers that support the proposed specifications. Carry-over of impurities has adequately been discussed. The solvents, auxiliary materials and reagents as well as the recovered raw materials are sufficiently specified. Adequate descriptions of the analytical methods and typical certificates of analysis for all raw materials used have been provided. Results of analysis have also been provided of the intermediate products that support the proposed specifications of the intermediates.

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. The MAH partly adopted the specifications and methods of the ASMF with additionally a specification for particle size distribution. A justification of the limit values and a description of the micronisation process have been provided and are acceptable. The relevance of impurities described in the monograph in the Ph. Eur has been discussed. The specification has been brought in line with Ph. Eur. monograph No. 2931. Batch analytical data demonstrating compliance with this specification have been provided for six batches.

Stability of drug substance

Stability data on the active substance have been provided for three batches stored at 30°C/65% RH (36 months) and 40°C/75% RH (six months) in accordance with applicable European guidelines. Based on the data submitted, a retest period could be granted of 36 months when stored in a two-layer polyethylene bag and then packaged in aluminium foil bags and then packaged in fibre drum tightly closed for transportation.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The formulation development is straightforward based on the composition of the reference product. As a fixed composition (including coating materials) and manufacturing process is applied, this compact development is considered acceptable.

Further formulation optimisations were performed by evaluating the solubiliser concentration, the particle size of the active substance and the selection of the coating material. Wet granulation was selected as the technological process of choice.

The MAH performed a bioequivalence study to compare the *in vivo* bioavailability of the test and innovator product. To support this study, *in vitro* comparative dissolution studies were performed. Overall, the dissolution of the proposed product and the reference product seems similar over the physiological range and in the proposed Quality Control (QC) method. The discriminatory nature of the QC dissolution test has been adequately demonstrated.

Manufacturing process

The manufacturing process comprises a straightforward blending, wet granulation, pre-compression blending, compression and coating of the tablet cores. The manufacturing process involving wet granulation is considered standard. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three full scale batches in accordance with the relevant European guidelines.

Control of excipients

Excipients comply with the Ph. Eur., except for the coating material, for which additional data have been provided. Some functionality related characteristics are controlled in the excipients Certificates of Analysis (CoA's) either by the finished product manufacturer or by the excipient supplier and, apparently are relevant for the quality of the drug product. In view of that, the tests for these characteristics have been included in the excipients specification. 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, uniformity of mass, uniformity of dosage units, related substances, dissolution, assay and microbiological

quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The MAH provided a risk evaluation and test results of additional production-size batches in order to justify non-routine testing for microbiological quality. Since the Ph. Eur. monographs for sorafenib tosylate and sorafenib tablets are now officially in force, the MAH has implemented Ph. Eur. monograph's nomenclature for impurities. Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three full scale batches from Manufacturer I and three full scale batches from Manufacturer II have been provided, demonstrating compliance with the specification.

Stability of drug product

Aluminium-OPA/Alu/PVC blisters

Results of 24 months storage at 25°C/60% RH have been submitted of three full-scale batches. Results of six months storage at 40°C/75% RH have been submitted of four batches including three full-scale batches. All results comply with the specifications and no clear trends have been observed.

Aluminium-PVC/PE/PVDC blisters

Results of 24 months storage at 25°C/60% RH, of 12 months storage at 30°C/65% RH, and of six months storage at 40°C/75% RH have been submitted of three full-scale batches. The results when stored for six months at 40°C/75% RH indicated out of specification results for X-ray powder diffraction (for two batches), while for all the other tested parameters the results obtained are well within specification. No significant changes were observed for tablets stored for 12 months at 30°C/65% RH and at 25°C/60% RH. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light.

Based on the data submitted, a shelf life was granted of 2 years. The labelled storage conditions are: "Do not store above 30°C".

Special precautions for disposal are: "This medicinal product could have potential risk for the environment. Any unused medicinal product or waste material should be disposed of in accordance with local requirements."

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

The component with possible TSE risk is magnesium stearate, however it is indicated that no materials of animal and/or human origin are contained or used in the manufacturing process of the medicinal product. Herewith, safety with respect to the possibility of transmitting TSE is considered justified.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Renixola 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 Renixola 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 Nexavar 200 mg, film-coated tablets, 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

Sorafenib tosylate 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.

For this generic application, the MAH has submitted two bioequivalence studies which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted one pilot and one pivotal bioequivalence study in which the pharmacokinetic profile of the test product Renixola 200 mg, film-coated tablets (Egis

Pharmaceuticals Plc, Hungary) is compared with the pharmacokinetic profile of the reference product Nexavar 200 mg, film-coated tablets (Bayer AG, Germany). Since the pilot study is considered as supportive, this study will not be discussed in this PAR.

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of the reference product with the test product. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study

- **Pivotal study under fasting conditions**

Design

A single-dose, randomised, four-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 72 healthy male subjects, aged 22-42 years. Each subject received a single dose (200 mg) of one of the two sorafenib tosylate formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least ten hours. There were four dosing periods. For group 1, the washout period was 14 days between periods 1 and 2 and between periods 3 and 4, while a washout period of 19 days was kept between periods 2 and 3. For group 2, the washout period was 16 days between periods 1 and 2, while a washout period of 14 days was kept between periods 2 and 3 and between periods 3 and 4 dosing.

Blood samples were collected pre-dose (within 1h prior to dosing) and at 0.5, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.50, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

Five subjects were withdrawn from the study. One subject did not report to the clinical facility for periods 2, 3 and 4 admission. Two subjects did not report to the clinical facility for periods 2, 3 and 4. One subject withdrew consent after period 4 dosing and the last subject was withdrawn from the study due to non-compliance to the protocol. 67 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of sorafenib tosylate under fasted conditions.

Treatment N=67	AUC_{0-72} (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	65804 ± 29110	2730 ± 1214	4.00 (1.00 – 12.00)
Reference	64087 ± 28705	2538 ± 1266	4.00 (1.33 – 24.00)
***Ratio (90% CI)**	1.03 (0.95 – 1.12)	1.10 1.01 – 1.20)	-
AUC_{0-72} area under the plasma concentration-time curve from time zero to 72 hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum concentration			

**ln-transformed values*

Conclusion on bioequivalence study
The pivotal study demonstrated that the 90% confidence intervals calculated for AUC_{0-72} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study, Renixola is considered bioequivalent with Nexavar.

The MEB has been assured that the bioequivalence studies have been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

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 Renixola.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	• Severe skin adverse events • Reversible posterior leukoencephalopathy syndrome (RPLS) • Hemorrhage including lung hemorrhage, gastrointestinal (GI) hemorrhage and cerebral hemorrhage • Arterial thrombosis (myocardial infarction) • Congestive heart failure (CHF) • Squamous cell cancer of the skin • Gastrointestinal perforation • Renal dysfunction • Interstitial lung disease-like events

	• Drug-induced hepatitis
Important potential risks	• Arterial thrombosis (cerebral ischemia) • Wound healing complications • Microangiopathy • Torsade De Pointes • Pregnancy and exposure through breastfeeding
Missing information	• None

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 Nexavar. No new clinical studies were conducted. The MAH demonstrated through two bioequivalence studies that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. 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 Felocord 5 mg and 7.5 mg film-coated tablets. 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

Renixola 200 mg, film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Nexavar 200 mg, film-coated tablets. Nexavar 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.

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 Renixola with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 11 August 2021.

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
NL/H/5391/001/IA/001	Type IA. B.II.e).5a).1.: Change in pack size of the finished product within the range of the currently approved pack sizes.	SmPC	30 December 2021	Approved	
NL/H/5391/001/IB/002	Type IB. B.II.f).1b). 1 Change in the shelf-life or storage conditions of the finished product; Extension of the shelf life of the finished product; as packaged for sale.	SmPC	29 December 2021	Approved	
NL/H/5391/001/IA/003	Type IA. B.II.b).4.a) Change in the batch size (including batch size ranges) of the finished product: Up to 10-fold compared to the originally approved batch size	-	24 December 2021	Approved	