COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Sorafenib GL 400 mg film-coated tablets (sorafenib)

NL/H/5169/001/DC

Date: 10 August 2021

This module reflects the scientific discussion for the approval of Sorafenib GL 400 mg film-coated tablets. The procedure was finalised at 29 April 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
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 Sorafenib GL 400 mg film-coated tablets, from G.L. Pharma GmbH.

Sorafenib GL is indicated for:

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

- Renal cell carcinoma
  Sorafenib GL 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 hybrid claiming essential similarity with the innovator product Nexavar 200 mg, film-coated tablets, which has been registered in the EEA by Bayer AG since 19 July 2006 through a centralised procedure (EMEA/H/C/000690).

The concerned member state (CMS) involved in this procedure was Austria.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, a hybrid application as the product has the same pharmaceutical form and composition as the reference medicinal product but different strength.

Similarity assessment in view of the orphan drug legislation
The MAH provided a similarity report in which potential similarity between Sorafenib GL 400 mg film-coated tables and the innovator Nexavar were discussed. Originally, Nexavar had two orphan indications: hepatocellular carcinoma and renal cell carcinoma (RCC). However, these orphan designations were withdrawn in July 2016 for RCC and in November 2017 for hepatocellular carcinoma. Nexavar has an additional indication: follicular thyroid cancer. This indication is currently under orphan market exclusivity. Therefore, this indication is not included in the product information of Sorafenib GL .
The indications for Sorafenib GL 400 mg film-coated tables are not infringing the market exclusivity of any Orphan Medicinal products with granted marketing authorisation.

II. QUALITY ASPECTS

II.1 Introduction

Sorafenib GL is a film-coated tablet. The tablets are white – off white and oval shaped, with a break line on one side and plain on the other side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses. Each tablet contains as active substance 400 mg of sorafenib, corresponding to 548 mg of sorafenib tosylate.

The tablets are packed in aluminium-OPA/Alu/PVC blisters.

The excipients are:
Tablet core - hypromellose 2910 (E464), croscarmellose sodium, cellulose, microcrystalline (E460), magnesium stearate (E470b) and sodium lauril sulfate
Tablet coating - hypromellose 2910 (E464), titanium dioxide (E171) and macrogol 3350 (E1521)

II.2 Drug Substance

The active substance is sorafenib tosylate, an established active substance. The substance is not yet described in the European Pharmacopoeia, but a draft monograph (2931) has been published in Pharmeuropa 31.2 (June 2019). Sorafenib tosylate is a white to slight yellow crystalline powder. The substance is very soluble in dimethylformamide and practically insoluble in methanol, acetonitrile or water. It exhibits polymorphism. The crystalline form III 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.

Manufacturing process
The manufacturing process consists over all of two synthesis steps, one saltification step and one purification step. The three proposed starting materials are acceptable. Results of analysis have been provided of batches starting material from all suppliers that support the proposed specifications. Carry-over of impurities has been adequately discussed. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised.

Quality control of drug substance

The drug product manufacturer adopted the specifications and methods of the active substance manufacturer, with additional specifications for identification of tosylates, particle size distribution and polymorphism. For the identification of tosylates, the high-performance liquid chromatography (HPLC) method for related substances of the active substance manufacturer is used. Compendial methods are used for particle size distribution and polymorphism. Batch analytical data demonstrating compliance with the drug substance specification have been provided for six commercial scale drug substance batches.

Stability of drug substance

Results of stability studies have been submitted of three batches (36 months at 30°C/65% RH and six months at 40°C/75% RH), in accordance with applicable European guidelines. Based on the data submitted, a retest period could be granted of 36 months. The shelf life is two years, without any special storage 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 are explained. The limit for particle size distribution of the drug substance is based on the drug substance batches used to manufacture the biobatch of the test product. Further formulation optimisation studies were performed by evaluating the solubiliser concentration, the particle size of the drug substance, the hardness, polymorphic stability and the selection of the coating material. Wet granulation was selected as the technological process of choice. The discriminatory nature of the quality control dissolution test has been adequately demonstrated.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. The manufacturing process is a standard process including wet granulation, compression, and film-coating. Process validation data on the product have been presented for three full scale batches in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with their respective Ph. Eur. monograph, except for the coating material. 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, identification of titanium dioxide, uniformity of mass, dimensions, uniformity of dosage units, related substances, dissolution, assay, subdivision of tablets and microbiological quality. The dissolution specification is in accordance with the Reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action. A risk

evaluation concerning the presence of nitrosamine impurities has been provided. Satisfactory validation data for the analytical methods have been provided. Batch analytical data of three full scale batches and one pilot scale batch from the proposed production site have been provided, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product have been provided for four batches, including one bio batch, in accordance with applicable European guidelines. All batches were stored in the commercial packaging of aluminium-OPA/Alu/PVC blisters. The results of 12 months storage at long term conditions have been submitted for three batches. For the bio batch, results have been submitted for up to six months storage at long term conditions. The results of six months storage at 40°C/75% RH have been submitted for all four stability batches. On basis of the data submitted, a shelf life was granted of 24 months. No specific storage conditions need to be included in the SmPC or on the label.

For the bulk film-coated tablets, results of 12 months storage at 25°C/60% RH have been submitted of two batches. The claimed shelf life of 12 months for the bulk film-coated tablets when stored at 25°C/60% RH could be granted.

Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light.

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

The component with possible TSE risk is magnesium stearate. It is however 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 Sorafenib GL 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 Sorafenib GL is intended for hybrid 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 hybrid 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 hybrid application, the MAH has submitted one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Sorafenib GL 400 mg film-coated tablets (G.L. Pharma GmbH, Austria) is compared with the pharmacokinetic profile of the reference product Nexavar 200 mg, film-coated tablets (Bayer AG, Germany).

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

Bioequivalence study

Design

A single-dose, randomised, four-period, two-treatment, two-sequence, fully replicate, crossover, oral bioequivalence study was carried out under fasted conditions in 64 healthy, adult, male subjects, aged 19-44 years. Each subject received a single dose (400 mg) of one of the two sorafenib formulations. The one tablet (test product) or two (reference product) tablets were orally administered with water after ten hours of fasting prior to dosing. There were four dosing periods, separated by washout periods of 20 days.

Blood samples were collected pre-dose and at 0.50, 1, 1.5, 2, 2.5, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 6, 7, 8, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products.
The design of the study is acceptable.

A bioequivalence study under fasted conditions is considered adequate as sorafenib has to be taken without food. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.
In the bioequivalence study, 400 mg of the test product is used versus 2 x 200 mg of the reference strength. For a hybrid application, this design 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

Two subjects discontinued because they did not report for check-in to the facility before dosing in Period II and III. The data of 62 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=62	**AUC_{0-72h} (ng/ml/hl)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	56701.8 ± 28249.4	2503.1 ± 1262.5	4.2 ± 1.5 (1.5-12)
Reference	51277.7 ± 28921.8	2176.7 ± 1177.8	4.6 ± 2.1 (2.5-12)
***Ratio (90% CI)**	1.12 (1.04-1.21)	1.15 (1.06-1.25)	-
Within-subject CV (%)	37.24	41.77	-

AUC_{0-72h}	area under the plasma concentration-time curve from time zero to t hours
C_{max}	maximum plasma concentration
t_{max}	time for maximum concentration
CV	coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence study

The within-subject variability of the reference product was 40.07% for the C_{max} based on data from 62 subjects. Based on the data of 62 subjects, the 90% confidence intervals of C_{max} is within the widened acceptance range of 0.75-1.34 and AUC_{0-72h} is within the acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study, Sorafenib 400 mg film-coated tablets are considered bioequivalent with Nexavar2×200 mg film-coated tablets.

The MEB has been assured that the bioequivalence study has 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 Sorafenib GL .

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 (ILD)-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 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. This hybrid 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 Nexavar 200 mg film-coated tablets (EMEA/H/C/000690), for the key messages, and Felocord 5 mg and 7.5 mg film-coated tablets (HU/H/0448/001-002/DC) for the design/layout. 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

Sorafenib GL 400 mg has a proven chemical-pharmaceutical quality and is a hybrid 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 Sorafenib GL with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 29 April 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/5167/001/IB/001	Type IB: B.II.b.1.e _ Addition of a bulk product manufacturer	NA	17 June 2021	Approval	