LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Sorafenib Mylan
sorafenib tosilate, sorafenib

SE/H/2271/001

This module reflects the scientific discussion for the approval of Sorafenib Mylan. The Public Assessment Report was written in August 2020 by the previous RMS (NL) after initial procedure NL/H/5057/001/DC and is attached at the end of this document. RMS transfer from NL to SE was completed 01-05-2022. For information on changes after this date please refer to the module 'Update'.

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Active substance	**sorafenib tosilate, sorafenib**
Pharmaceutical form	**Film-coated tablet**
Strength	**200 mg**
Applicant	**Mylan AB**
EU-Procedure number (original)	**NL/H/5057/001/DC**

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Sorafenib Mylan 200 mg, film-coated tablets

(sorafenib tosylate)

NL/H/5057/001/DC

Date: 6 August 2020

This module reflects the scientific discussion for the approval of Sorafenib Mylan. The procedure was finalised on 3 June 2020. 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
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
XRD	X-Ray Diffraction

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Sorafenib Mylan 200 mg, film-coated tablets from Mylan B.V.

The product is indicated for:

- Hepatocellular carcinoma
  Sorafenib Mylan is indicated for the treatment of hepatocellular carcinoma.

- Renal cell carcinoma
  Sorafenib Mylan 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 by Bayer AG since 19 July 2006 through a centralised procedure (EU/1/06/342/001).

The concerned member states (CMS) involved in this procedure were Bulgaria, Croatia, Czech Republic, Denmark, Finland, France, Germany, Hungary, Iceland, Italy, Poland, Portugal, Romania, Slovakia, Spain and the UK.

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

II. QUALITY ASPECTS

II.1 Introduction

Sorafenib Mylan 200 mg is a red-brown, round, biconvex film-coated tablet, debossed with "200" on one side and plain on the other side. Each film-coated tablet contains 200 mg of sorafenib (as tosylate).

The film-coated tablets are packed in Aluminium-PVC/PE/PVDC blisters or Aluminium-OPA/Alu/PVC blisters.

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

Tablet coating - hypromellose 2910 (E464), titanium dioxide (E171), macrogol (E1521), red iron oxide (E172)

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 (No. 2931) has been published in Pharmeuropa 31.2 (June 2019). The active substance is a white to slight yellow crystalline powder. Sorafenib tosylate is very soluble in DMF and practically insoluble in methanol, acetonitrile or water. The active substance has no asymmetric carbons. It exhibits polymorphism. 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 of the drug substance is described in detail. Reaction sequences and process flow charts are provided together with a detailed narrative of the manufacturing process. Reprocessing in case that the intermediates or the drug substance do not comply with the valid specification is acceptably described. The three proposed starting materials are acceptable. 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 MAH adopted the specifications and methods of the ASMF with additional specifications for identification of tosylates and particle size distribution.
The description of the micronisation process, the control method and its validation have been provided. The relevance of impurities described in the draft Monograph in Pharmeuropa has been discussed. Moreover, the proposed specifications are in line with the Draft Ph. Eur. Monograph. The provided batch analysis data of six production scale batches demonstrate compliance with the drug substance specification.

Stability of drug substance
Results of stability studies have been submitted of three batches (36 months at 30 ± 2°C/65 ± 5 % RH and 6 months at 40 ± 2ºC/75 ± 5 % RH) that support the retest period of 36 months. Information on the analytical methods applied in the stability studies has been provided.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. Further formulation optimizations were performed by evaluating the solubilizer 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.
Polymorphic form III is used. A drug substance control is set. Changes of this form over manufacture and storage of the drug product have not been observed. The proposed three-tier specification for particle size distribution is acceptable.
Solubility of the drug substance in aqueous media over the pH range is low and sink conditions are marginally satisfied only in dissolution medium 0.1N HCl + 1% SLS. The proposed dissolution method is the same as described in the Draft Ph. Eur. monograph for sorafenib tablets. 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 has adequately been described and validated. It is considered a standard process.
Results of process validation have been provided of three full-scale batches.

Control of excipients
The excipients comply with the Ph. Eur., except for the coating material, for which additional data are requested. The specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identification, uniformity of mass, dimensions, uniformity of dosage units, related substances, dissolution, assay and microbiological quality. The proposed stricter limits for impurities are acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three full-scale batches and one pilot-scale batch, demonstrating compliance with the release specification.

Stability of drug product
Aluminium-OPA/Alu/PVC blisters: Results of 18 months storage of two full-scale batches and results of 12 months storage of one full-scale batch and one lab-scale batch at long-term conditions have been submitted. Results of 6 months storage at 40°C/75% RH have been

submitted of four batches including three full-scale batches. All results comply and no clear trends have been observed.
Aluminium-PVC/PE/PVDC blisters: Results of 18 months storage of two full-scale batches and results of 12 months storage of one full-scale batch and one lab-scale batch at long-term conditions have been submitted. Results of 12 months storage at 30°C/65% RH have been submitted of four batches including three full-scale batches. Results of 6 months storage at 40°C/75% RH have been submitted of four batches including three full-scale batches. The results when stored for 6 months at 40°C/75% RH indicated out of specification results for XRD, while for all the rest tested parameters all the results obtained are well within specification. No significant changes were observed for tablets stored 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 provided data and based on extrapolation, a retest period of 24 months without any special storage conditions (Aluminium-OPA/Alu/PVC blisters) or 24 months with a storage condition "Do not store above 30°C" (Aluminium-PVC/PE/PVDC blisters) have been granted.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded. Magnesium stearate is derived from vegetable origin.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Sorafenib Mylan 200 mg 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 Mylan 200 mg 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, 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 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 the results of one pilot bioequivalence study and one pivotal bioequivalence study, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence studies in which the pharmacokinetic profile of the test product Sorafenib Mylan 200 mg (Mylan B.V., the Netherlands) 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 studies is justified, as Nexavar is authorised through a centralised procedure. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

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.

Bioequivalence studies
Pilot study
A single-dose, open label, balanced, randomised, four-period, four-treatment, four-sequence, crossover bioequivalence study was carried out under fasted conditions in 24 healthy adult male subjects. Being a pilot study its objective was to compare and evaluate the single-dose oral comparative bioavailability of 3 test formulation of Sorafenib Mylan 200 mg tablets and the marketed product Nexavar. Twenty-two subjects completed the study and were eligible for pharmacokinetic analysis.

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

Treatment N=22	AUC_{0-72} (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	59.04 ± 30.70	2.46 ± 1.264	3.67 (1.67–4.67)	--
Reference	56.61 ± 25.50	2.22 ± 1.00	4.00 (3.00–12.00)	--
***Ratio (90% CI)**	1.02 (0.84–1.25)	1.08 (0.89 – 1.30)	--	--
CV (%)	--	--	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life
CV coefficient of variation

**ln-transformed values*

Pivotal study

Design

A single-dose, open label, balanced, randomised, four-period, two-treatment, two-sequence, crossover full replicate 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 2 sorafenib formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were 4 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 periods 2 and 3 and between periods 3 and 4 dosing.

Blood samples were collected pre-dose 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. The procedures followed for a fasting study are according to the bioequivalence guideline. The sampling time period until 72 hours post-dose is sufficient to determine and provide a reliable estimate of the extent of exposure for this immediate-release product as the absorption phase is covered. The frequency of sampling around the peak concentration of sorafenib is adequate to determine the t_{max} accurately. The wash-out period of at least 14 days is sufficient to prevent carry-over effects considering that this was more than 5x the half-life of sorafenib (i.e. 25 – 48 hours).

Results
Group 1 – One subject did not report to the clinical facility for periods 2, 3 and 4 admission,
Group 2 – Two subjects did not report to the clinical facility for periods 2, 3 and 4; one subject 32 withdrew consent after period 4 dosing; one subject due to non-compliance as per protocol.
Sixty-seven subjects were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax (median, range)) of sorafenib under fasted conditions.

Treatment N=67	**AUC_{0-72}** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)	**$t_{1/2}$** (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)	--	--
CV (%)	--	--	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life
CV coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence studies
Results of the pilot study showed that the AUC0-72h met the required range of 0.80-1.25 while the Cmax exceeded the upper limit (1.2985). However, high variability has been observed and the power calculated for C_{max} and AUC_{0-72h} was found equal to 61.95% and 58.51% respectively. The number of subjects (n=22) included is therefore not sufficiently powered to conclude bioequivalence.

In the pivotal study the intrasubject variability of the reference product has been shown to be above 30% (i.e. 35.12%) and a widening of the acceptance range for Cmax to 77.17 – 129.59%, as pre-specified, would be applicable. However, with 67 subjects completed and with a power of more than 80% for AUC_{0-72} (99.40%) and C_{max} (99.82%), the standard range of 0.80-1.25 has been adequately met for both AUC and C_{max}. Based on the submitted pivotal study Sorafenib Mylan 200 mg is considered bioequivalent with Nexavar 200 mg.

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 Sorafenib Mylan.

Table 3. Summary table of safety concerns as approved in RMP

Important identified risks	• Severe skin adverse events • Hand-foot skin reaction (HFSR) • Hypertension • 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 • Symptomatic pancreatitis and increases in lipase and amylase • Hypophosphatemia • Safety and efficacy in patients with non-small cell cancer of the lung (NSCLC) with squamous histology • 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
Missing information	• Safety in children and adolescents • Safety and efficacy in patients with HCC and Child-Pugh B liver dysfunction

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 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, referring to the PL for Felocord 5 mg and 7.5 mg film-coated tablets. Based on similarities in the format, design, layout and wording of the PLs, bridging of the PL for Sorafenib 200 mg film-coated tablets to the PL of Felocord 5 mg and 7.5 mg film-coated tablets is considered acceptable for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Sorafenib Mylan 200 mg, film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Nexavar 200 mg. 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 Mylan with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 3 June 2020.

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