21 October 2022
EMA/834802/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Sorafenib Accord

International non-proprietary name: sorafenib

Procedure No. EMEA/H/C/005921/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AEs : Adverse events

AMPC : 4-(4-aminophenoxy)-N-methyl-2-pyridinecarboxamide

ARCCS : Advanced Renal Cell Carcinoma Sorafenib

ASMF : Active Substance Master File = Drug Master File

AUC 0-∞ : Area under the plasma concentration versus time curve from time zero to infinity

AUC0-t : Area under the plasma concentration versus time curve from time

zero to the last measurable concentration

BCS : Biopharmaceutics Classification System

BP : Blood pressure

CBC : Complete blood count

CHF : Congestive heart failure

Cmax : Maximum measured concentration of drug in plasma

CP : Child-Pugh

CR : Complete response

CT : Computed Tomography

CV : Cardiovascular

CYP : Cytochrome P

DCS : Differential Scanning Calorimetry

DTCs : Differentiated thyroid carcinomas

EC : Endothelial cell

EC : European Commission

ECG : Electrocardiogram

ECOG : Eastern Cooperative Oncology Group

eGFR : Estimated glomerular filtration rate

ELISA : Enzyme-linked immunosorbent assay

EMA : European Medicines Agency

EU : European Union

FAS : Full-analysis set

FDG : Fluorodeoxyglucose

FT-IR : Fourrier Transform Infrared Spectroscopy

GC : Gas Chromatography

HCC : Hepatocellular carcinoma

HDPE : High Density Polyethylene

HFSR : Hand–foot skin reaction

HR : Hazard ratio

IC50 : Median inhibitory concentration

ICH : International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

IR : Infrared

KF : Karl Fischer titration

MAA : Marketing Authorization Application

mg : Milligram

ml : Milliliter

MRI : Magnetic resonance imaging

MTC : Medullary thyroid carcinoma

NCI-CTC : National Cancer Institute Common Toxicity Criteria

nM : Nanometer

NLT : Not less than

NMR : Nuclear Magnetic Resonance

NO : Nitric oxide

OS : Overall survival

PET : Positron emission tomography

PFS : Progression-free survival

Ph. Eur. : European Pharmacopoeia

PK : Pharmacokinetic

PR : Partial response

PSD : Particle size distribution

PTC : Papillary thyroid carcinoma

PXRD : Powder X-ray diffraction

RAI : Radioiodine

RCC : Renal cell carcinoma

RECIST : Response Evaluation Criteria in Solid Tumors

RR : Risk ratio

QbD : Quality by design

QC : Quality Control

RH : Relative Humidity

SD : Stable disease

SLS : Sodium laurilsulfate

SmPC : Summary of product characteristics

t1/2 : Elimination half-life

Tg : Thyroglobulin

TGA : Thermo-Gravimetric Analysis

TKI : Tyrosine kinase inhibitor

TKRs : Tyrosine kinase receptors

tmax : Time to reach the maximum concentration of drug in plasma

TTF : Time to treatment failure

UV : Ultraviolet

Vd : Volume of distribution

VEGF : Vascular endothelial growth factor

µM : Micrometer

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Accord Healthcare S.L.U. submitted on 28 June 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Sorafenib Accord, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 22 April 2021.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication.

Sorafenib Accord is indicated for:

- the treatment of hepatocellular carcinoma
- 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

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Nexavar instead of non-clinical and clinical unless justified otherwise.

The chosen reference product is: Nexavar 200 mg film coated tablets

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

- Product name, strength, pharmaceutical form: Nexavar 200 mg film coated tablets
- Marketing authorisation holder: Bayer AG
- Date of authorisation: 19-07-2006
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/06/342/001

Medicinal product authorised in the Union /Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Nexavar 200 mg film coated tablets
- Marketing authorisation holder: Bayer AG

- Date of authorisation: 19-07-2006
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/06/342/001

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Nexavar 200 mg film coated tablets
- Marketing authorisation holder: Bayer AG
- Date of authorisation: 19-07-2006
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/06/342/001

1.2. Information on paediatric requirements

Not applicable

1.3. Information relating to orphan market exclusivity

1.3.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.4. Scientific advice

The applicant did not seek Scientific advice from the CHMP.

1.5. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP were:

Rapporteur: Hrefna Gudmundsdottir

The application was received by the EMA on	28 June 2021
The procedure started on	15 July 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	5 October 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	18 October 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	11 November 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	18 February 2022
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	29 March 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	07 April 2022
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	22 April 2022
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	21 June 2022
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	29 August 2022
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Sorafenib Accord on	15 September 2022

2. Scientific discussion

2.1. Introduction

Sorafenib is a multikinase inhibitor that decreases tumour cell proliferation *in vitro*. Sorafenib inhibits tumour growth of a broad spectrum of human tumour xenografts in athymic mice accompanied by a reduction of tumour angiogenesis. Sorafenib inhibits the activity of targets present in the tumour cell (CRAF, BRAF, V600E BRAF, c-KIT, and FLT-3) and in the tumour vasculature (CRAF, vascular endothelial growth factor receptor-2

(VEGFR-2), vascular endothelial growth factor receptor-3 (VEGFR-3), and PDGFR-ß). RAF kinases are serine/threonine kinases, whereas c-KIT, FLT-3, VEGFR-2, VEGFR-3, and PDGFR-ß are receptor tyrosine kinases.

The pharmacotherapeutic group of Sorafenib is Antineoplastic agents, protein kinase inhibitors, ATC code: L01EX02

This centralized application concerns a generic application according to article 10(1) of Directive 2001/83/EC for Sorafenib Accord 200 mg film-coated tablets. The applicant is Accord Healthcare S.L.U.

The originator product is Nexavar 200 mg film coated tablets, marketed by Bayer AG and registered within the community since 19 July 2006. A pilot bioequivalence (BE) study was carried out using the originator as reference product sourced from Germany (Study Number 0320-20).

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 200 mg of sorafenib tosilate as active substance. The product contains the ester sorafenib tosilate.

Other ingredients are:

Tablet core: croscarmellose sodium, microcrystalline cellulose, hypromellose, sodium laurilsulfate, magnesium stearate

Film-coat: hypromellose (E464), macrogol (E1521), titanium dioxide (E171) and ferric oxide red (E172)

The product is available in Aluminium-Aluminium perforated unit dose blisters as described in section 6.5 of the SmPC.

2.2.2. Active substance

2.2.2.1. General Information

The chemical name of Sorafenib tosilate is 4-[4-[[[4-Chloro-3-(trifluoromethyl)phenyl]carbamoyl] amino]phenoxy]-N-methylpyridine-2-carboxamide 4-methylbenzene-1-sulfonate corresponding to the molecular formula $C_{28}H_{24}ClF_3N_4O_6S$. It has a molecular mass of 637 g/mol and the following structure:

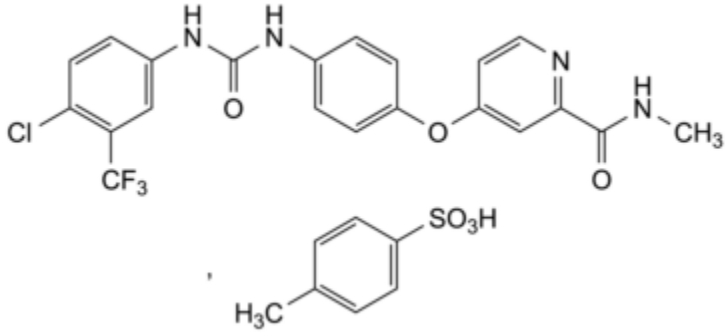

Figure 1: active substance structure

The chemical structure of the active substance was elucidated by a combination of elemental analysis, ^{1}H and ^{13}C NMR spectroscopy, UV spectroscopy, FT-IR study and mass spectrometry. The solid state properties of the active substance were measured by thermal analysis (DSC) and thermogravimetric analysis (TGA).

The active substance, sorafenib tosilate, is a white or slightly yellowish or brownish powder. It is practically insoluble in water, slightly soluble in anhydrous ethanol and practically insoluble in heptane. Sorafenib tosilate has a non-chiral molecular structure, therefore does not show any optical isomerism. It is not hygroscopic and is classified as a BCS Class II compound with a low solubility and high permeability.

According to the literature sorafenib tosilate exhibits different polymorphisms (Form I, Form II, Form III).The polymorphic form produced by the active substance manufacturer has been described. It has been demonstrated that the proposed manufacturing process consistently produces this form. This form is shown stable and does not convert during manufacturing process or storage. Polymorphic form is routinely controlled by PXRD as part of the active substance specification.

2.2.2.2. Manufacture, characterisation and process controls

The active substance is supported by an ASMF. Sorafenib tosilate is manufactured using well defined starting materials with acceptable specifications by one manufacturer, and all steps are performed at the same site. The manufacturing process is described in three steps, two synthetic and one final salification step where the tosilate salt is formed. Micronisation is performed at the active substance manufacturer to achieve the required particle size.

During the procedure, two major objections (MOs) were raised related to the control and acceptability of the starting materials. As a response, the overall control strategy related to the proposed starting materials has been significantly improved and specification limits for impurities tightened and adequately justified. Based on the improved control strategy and confirmation of the commercial availability, the starting materials are considered justified and in line with ICH Q11 and are accepted by the CHMP.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised. A MO was raised regarding the alkyl tosilate impurities origin, related test method and lack of set specifications. The applicant has provided additional information on the origin and justified the

use of in-house HPLC method instead of Ph. Eur. method. Limits have been added to the specification and skip-test justified, leading to a resolution of the MO.

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

The active substance is packaged in double polyethylene bags, placed in triple laminated bag, and finally placed in a HDPE container. The material complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

2.2.2.3. Specification(s)

The active substance specification includes tests for description, solubility (Ph. Eur.), identification (IR, HPLC), para toluene sulfonic acid content (in-house/Ph. Eur.), water content (coulometric titration, Ph. Eur.), sulphated ash (Ph. Eur.), related substances (HPLC), assay (HPLC), residual solvents (GC), polymorphic identification (PXRD), particle size (in-house), content of methyl, ethyl and isopropyl P-toluene sulphonate (in-house/Ph. Eur.).

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data for three production scale batches of the active substance from the active substance manufacturer and two from the finished product manufacturer are provided. The results are within the specifications and consistent from batch to batch.

The control tests were carried out to comply with the specifications and test methods of the Ph. Eur. Monograph (04/2021:2931). The applicant adopted the Ph. Eur. monograph and its methods except for tosilate esters. For testing of tosilate esters, the in-house quantitative method is used and validated. The batch data comparison is provided, and the methods can be considered equivalent.

The proposed active substance specification is in line with the Ph. Eur. monograph for sorafenib tosilate, or contains tighter limits (impurities A, D, and unspecified impurities) than stated in the monograph. Additional specifications have been set for the para toluene sulfonic acid content, residual solvents, polymorphic identification and methyl, ethyl and isopropyl P-toluene sulphonate content. All additional methods have been adequately validated and described according to ICH Q2.

2.2.2.4. Stability

Stability data from three production scale batches of active substance from the proposed manufacturer stored in a container closure system representative of that intended for the market for up to 60 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested: appearance, identity, water content, impurities, assay and polymorphic identification. The analytical methods used were the same as for release and were stability indicating.

All tested parameters were within the specifications, with no noticeable trends in any of the quality attributes tested, including polymorphic form. is the same results are additionally confirmed by the stability data of one micronised batch.

Photostability testing following the ICH guideline Q1B was performed on 1 batch. The substance is not photosensitive. Results on stress conditions (elevated temperature and relative humidity, water, acid and base hydrolysis, oxidation) were also provided. The active substance is found stable under thermal and relative humidity conditions and after exposure to water hydrolysis and is sensitive to acid, base and oxidation conditions.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 60 months in the proposed container without specific storage conditions.

2.2.3. Finished medicinal product

2.2.3.1. Description of the product and Pharmaceutical development

The finished product is a 200 mg film-coated tablet. Tablets are red, round, biconvex, bevel-edged, 12.0 mm in diameter, debossed with "H1" on one side and plain on other side. Each tablet contains 44.3% of the active substance as tosilate salt or 32% of Sorafenib.

The aim of the pharmaceutical development was to develop a generic product similar to the reference product. The first step of the development was to explore physical and chemical characteristics of the reference product. The reference product Nexavar 200 mg film-coated tablets was evaluated for chemical characteristics such as assay, related substances and dissolution. The same excipients as those used in the reference product were selected and various studies performed to optimise the formulation and the process parameters, as summarised below.

The manufacturing process development is considered as standard, no Quality by Design (QbD) or Design space is used. Different formulations were made where dissolution, disintegration, and resistance to crushing were used to guide the development. Trails were taken, observing the effect of using different quantities of disintegrant, binder, lubricant and water of granulation. Manufacturing process studies were undertaken to optimise the process. Development batches were made at different conditions (differences in granulation, blending and lubrication time, binder addition, kneading time) and tested for physical characteristics, dissolution and blend uniformity. Additionally, the compression machine speed challenge was performed to evaluate the effect of machine speed on physicochemical characteristics of the tablets and the hardness challenge was performed to evaluate the effect of compression force. To evaluate impact of active substance particle size distribution (PSD), trials were taken with active substance with different PSD. Within the specified PSD acceptance criteria, no significant impact on dissolution was observed. The particle size specification for active substance is set in line with biobatch data and trend results of the production scale active substance batches.

One of the main objectives of the pharmaceutical development was designing a suitable and discriminatory dissolution QC method. The pH-solubility profile indicated very low solubility of sorafenib tosilate in the different studied media.. Different concentrations of the surfactant were studied and a complete release was observed with the selected concentration of surfactant. Based on the studied data, the QC dissolution methods conditions were defined .

The bioequivalence study was performed between the reference product Nexavar 200 mg film-coated tablets and the test product Sorafenib Tablets 200 mg. Based on the presented bioequivalence study the test product

is considered bioequivalent with the reference product. The formulation used in the study was the same as that intended for marketing and was made according to the proposed manufacturing process. The formulation of the test product has the same composition as the reference product, same excipients are used.

Dissolution profiles of the products used in the bioequivalence study have been compared in 900 ml 0.1N HCl, acetate buffer (pH 4.5) and phosphate buffer (pH 6.8) with surfactant, applying f_2 statistics method. The dissolution profiles of the test and reference product were demonstrated similar over the physiological range and in the proposed QC method. The discriminatory power of the dissolution method has been demonstrated.

After submission of the MAA the Ph. Eur. finished product monograph for sorafenib tablets (01/2022:3022) was published, hence, a MO was raised requesting to demonstrate that the proposed method complies with the Ph. Eur. dissolution method or, alternatively, to adopt it. Additionally, the same MO, requested to set the dissolution acceptance criteria on the biobatch and in line with the EMA´s reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action EMA/CHMP/CVMP/QWP/336031/2017. As a response, the applicant adopted the Ph. Eur. method for dissolution and tested the finished product in line with the Ph. Eur. method, demonstrating compliance with the Ph. Eur. monograph for sorafenib tablets. for release and shelf-life specifications. Adopting the Ph. Eur. dissolution method and tightening of the dissolution acceptance criteria resulted in resolution of the major objection.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards, with exception of the film-coating material ferricoxide (E172), which is compliant with the EU food regulation. There are no novel excipients used in the finished product formulation. A detailed compatibility study was performed where the active substance was mixed with an excipient and stored. Compatibility has been sufficiently demonstrated and supported with the long term and accelerated stability data. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.2.1 of this report.

The polymorphic form of the active substance in the finished product was monitored for 6 months at 40°C/75%RH and compared with the placebo and active substance. It was confirmed that the polymorphic form is stable and does not convert during the manufacturing process or storage.

Primary packaging material selection was based on similar product development experience and stability studies. The primary packaging is Aluminium-Aluminium perforated unit dose blister as stated in the SmPC. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.2.3.2. Manufacture of the product and process controls

The manufacturing process consists of following main steps: co-sifting, dry mixing, wet granulation, drying, sifting/milling, blending, lubrication, compression, film-coating and packaging. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated on three production scale batches. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

2.2.3.3. Product specification(s)

The finished product release and shelf-life specifications shown in **Error! Reference source not found.** include appropriate tests for this kind of dosage form including description (visual), average weight (in-house), identification (HPLC, UV), water content by KF (Ph. Eur.), dissolution by UV (Ph. Eur.), related substances by HPLC (Ph. Eur.), uniformity of dosage units by mass variation (Ph. Eur.), assay by HPLC (Ph. Eur.) and microbiological quality (Ph. Eur.).

As a Ph. Eur. monograph for the active substance and finished product are now available, a MO was raised regarding the used in-house analytical methods and proposed finished product specifications. The applicant was asked to demonstrate equivalence of the in-house methods with the Ph. Eur. methods or to adopt the Ph. Eur. methods. Additionally, the finished product specifications were asked to be set in compliance with the Ph. Eur. finished product monograph for sorafenib tablets (01/2022:3022). The MO was resolved, as the applicant adopted the Ph. Eur. monograph methods and specifications.

The finished product specification covers appropriate parameters for this dosage form and comply with the Ph. Eur. monograph Sorafenib tablets (01/2022:3022). The dissolution acceptance criteria are tighter in comparison to the monograph, set in line with the biobatch. The batch analysis results show that the finished product meets the proposed specification and the Ph. Eur. monograph.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods are adopted from the Ph. Eur. monograph for sorafenib tablets (01/2022:3022), including quantitative methods for dissolution, assay and related substances. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for three production scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

2.2.3.4. Stability of the product

Stability data from three production scale batches of finished product stored for up to 24 months under long term conditions (25°C / 60% RH) and for up to 6 months under accelerated conditions (40°C / 75% RH) according to the ICH guidelines were provided. The batches of the finished product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. Samples were

tested for water content, dissolution, related substances, assay and microbiological quality. The analytical methods used are stability indicating. No significant changes have been observed in any of the parameters tested at the long term and accelerated conditions. Minor fluctuations have been observed for the water content; however, the values are well within the set specifications and considered stable. Further, three bulk storage batches have been added to the stability program, packed in triple laminated aluminium bag. The stability data shows that the bulk is stable for 12 months at long term conditions and 6 months at accelerated conditions.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No changes were observed, the finished product is not photosensitive. A forced degradation study (acid, base, oxidative, heat, humidity, photolytic and metal ions degradation) was carried out as part of the analytical method validation in order to prove the specificity of the HPLC method for assay and related substances in the finished product, and therefore the stability indicating capability of those methods. The product is stable towards degradation, supported by low values for impurities. No significant degradation was observed under the acid, base, oxidative, heat, humidity, photolytic and metal ions degradation conditions. The results from the forced degradation study demonstrate that the methods are stability indicating.

Based on available stability data, the proposed shelf-life of 24 months with no special storage conditions as stated in the SmPC (section 6.3 and section 6.4) is acceptable.

2.2.3.5. Post approval change management protocols

N/A

2.2.3.6. Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.
The active substance (sorafenib tosilate) and the finished product sorafenib tablets are subject of a Ph. Eur. Monograph, with which they comply. The finished product has been developed as a generic of Nexavar 200 mg film-coated tablets.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The MOs relating to the choice of starting materials were resolved based on the improved control strategy and confirmation of the commercial availability. The MO regarding the active substance impurities was resolved by providing additional information on origin, applying additional control strategy, and providing adequate justification of the used method. Finally, during the procedure, the applicant has adopted Ph. Eur. finished product monograph for Sorafenib tablets and tightened dissolution acceptance criteria, to resolve the MOs related to the finished product.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

N/A

2.3. Non-clinical aspects

2.3.1. Introduction

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. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Pharmacodynamic, pharmacokinetic and toxicological properties of sorafenib are well known. As sorafenib 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

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Sorafenib Accord by Accord Healthcare S.L.U., Spain is considered unlikely to result in any significant increase in the combined sales volumes for all sorafenib containing products and the exposure of the environment to the active substances. Thus, the ERA is expected to be similar and not increased.

2.3.3. Conclusion on the non-clinical aspects

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate. The application contains an adequate review of published non-clinical data.

The non-clinical sections of the SmPC are in line to that of the brand leader product.

There are no objections to the approval of Sorafenib Accord from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for film-coated tablets containing sorafenib. To support the marketing authorisation application the Applicant conducted one bioequivalence study with cross-over design under fasting conditions.

No formal scientific advice by the CHMP was given for this medicinal product. For the clinical assessment, Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1) as well as the Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/09) and the Sorafenib film-coated tablets 200 mg product-specific bioequivalence guidance (EMA/CHMP/315232/2014 Rev.1*) are of particular relevance.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC

Clinical studies

To support the application, the applicant has submitted 1 bioequivalence study for the 1 strength applied (Study Number 0320-20).

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

Study Number 0320-20

This was an open label, balanced, randomized, two-treatment, four-period, two-sequence, single oral dose, fully replicate, crossover, bioequivalence study of Sorafenib Tablets 200 mg with Nexavar® tablets 200 mg of Bayer AG, Kaiser- Wilhem- Allee, 51368, Leverkusen, Germany in normal healthy, adult, human subjects under fasting condition.

Methods

Study design

The study was open label, balanced, randomized, two-treatment, four-period, two-sequence, single oral dose, fully replicate, crossover, bioequivalence study comparing two sorafenib (test product and reference product) 200 mg film-coated tablet formulations in 64 healthy adult subjects under fasting conditions. The study was conducted under standardised conditions. Sorafenib was measured in human plasma using a validated LC-MS/MS method.

Population(s) studied

64 healthy adult male subjects (19 - 44 years old, BMI 18.77 – 29.89 kg/m2) of Asian race were enrolled and randomized. After withdrawals/discontinued subjects during the study 52 subjects completed all the periods

of the clinical phase of the study successfully.

Analytical methods

A validated LC-MS/MS method, using protein precipitation method for extraction, was used to determine Sorafenib concentrations in K2EDTA human plasma.

The internal standard was Sorafenib 13CD3. Certificates of analysis were provided for the analyte and the internal standard.

The calibration curve range during study sample analysis was from 20.003 to 6003.476 ng/ml. The quality control concentrations (ng/ml) were LOQ QC = 20.881, LQC = 59.660, INTQC = 180.242, LMQC = 870.737, MQC = 1892.906, HQC = 4792.166 and DQC = 17990.929.

Accuracy and precision of QC samples for sorafenib obtained during analysis of subject samples is shown below:

Sorafenib in Human plasma (ng/mL) (refer to Table No. 03)					
QC Ids	HQC	MQC	LMQC	INTQC	LQC
Precision (% CV)	2.6	2.4	2.4	4.8	6.4
Accuracy (%)	102.0	103.7	106.2	100.8	103.4
Nominal Value	4792.166	1892.906	870.737	180.242	59.660

Table 1

A total of 5592 samples were analysed. The Number of reinjections was 153. Two (02) samples (0.04%) were reanalysed due to following reasons: 1) Concentration above highest standard 2) Significant variations in response of internal standard. For incurred sample reanalysis 358 samples were run. 100 % of samples were found to be within a variation of 20% from the mean value. Long term stability at -65 ± 10°C was proven for a period that spanned the time from first study sample collection to completion of ISR analysis.

Pharmacokinetic variables

The pharmacokinetic parameters were calculated from the plasma concentration vs. time profile by non-compartmental model using Phoenix® WinNonlin® Version 8.1 (Certara L.P.) for sorafenib.

Primary pharmacokinetic parameters were Cmax and AUC0-72

Secondary pharmacokinetic parameter was Tmax

Statistical methods

PROC GLM of SAS® Version 9.4 (SAS Institute Inc., USA) was employed for statistical analysis. ANOVA was performed on ln-transformed pharmacokinetic parameters Cmax and AUC0-72.

ANOVA model included Sequence, Subject (Sequence), Formulation and Period as fixed effects. The ln-transformed pharmacokinetic parameters (Cmax and AUC0-72) of Sorafenib were analysed using an ANOVA model at alpha 0.05.

Bioequivalence criteria:

Based on the statistical results of 90% confidence interval for the ratio of the geometric least squares means for ln-transformed pharmacokinetic parameters Cmax and AUC0-72; conclusion was drawn for Test Product-T vs. Reference Product-R for Sorafenib with following considerations:

For AUC0-72: If the 90% confidence interval of geometric least square mean ratio of Test to Reference falls within the acceptance range of 80.00–125.00% for ln-transformed pharmacokinetic parameter AUC0-72.

For Cmax:

1) If within-reference intra-subject CV of ln-transformed pharmacokinetic parameter Cmax ≤ 30% then bioequivalence of the test product with that of the reference product was concluded, if the 90% confidence interval fell within the acceptance range of 80.00–125.00% for ln-transformed pharmacokinetic parameter Cmax.

2) If within-reference intra-subject CV of ln-transformed pharmacokinetic parameter Cmax > 30% then BE limit was widen using scaled-average bioequivalence. Under scaled-average-bioequivalence, [U, L] = exp [±k·SWR], where U was the upper limit of the acceptance range, L was the lower limit of the acceptance range k was the regulatory constant set to 0.760 and SWR was the within-subject standard deviation of the ln transformed values of Cmax of the reference product.

3) If within-reference intra-subject CV of ln-transformed Cmax ≥ 50% then Cmax limit was widen maximum up to 69.84 to 143.19%.

Bioequivalence of the test product with that of the reference product was concluded for Cmax, if both of the following conditions were satisfied:

i) The 90% confidence interval for ln-transformed data of Cmax fell within the newly widen range [U, L] = exp [±k·SWR], which was based upon the within-subject variability of reference product observed for Cmax.

ii) ii) The geometric least square mean ratio (GMR) of test to reference for Cmax fell within the acceptance range of 80.00–125.00%.

Results

Pharmacokinetic results (for 59 subjects who were included in statistical analysis) and the statistical analysis are showed in the tables below.

Pharmacokinetic parameters for Sorafenib (non-transformed values)

Pharmacokinetic parameter	Test (N = 114 Observations)		Reference (N = 114 Observations)	
	arithmetic mean	SD	arithmetic mean	SD
$AUC_{(0-72h)}$, ng.h/mL	34492.137	18006.9289	34291.266	21848.0980
C_{max} , ng/mL	1834.780	1058.3982	1694.308	1062.7943
T_{max}*, hour (h)	4.000 (2.000 - 24.000)	-	4.000 (2.500 - 7.000)	-
AUC_{0-72h} area under the plasma concentration-time curve from time zero to 72 hours C_{max} maximum plasma concentration T_{max} time for maximum concentration (* median, range)				

Table 2

Statistical analysis for Sorafenib (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference (%)	Confidence Intervals	Acceptance Criteria (%)	CV%*
$AUC_{(0-72h)}$	103.8	95.18 – 113.26	80.00- 125.00	42.8
C_{max}	109.1	99.29 – 119.89	71.14 – 140.56	47.1
* estimated from the Residual Mean Squares				

Table 3

The acceptance criteria for Cmax were widened based on the extent of the intra-subject standard deviation of the ln-transformed value of Cmax of the reference product observed. The study confirmed high intra-subject variability of Cmax for the test and reference product. However, widened acceptance criteria were not necessary as all results fell within the conventional acceptance criteria of 80.00-125.00% for Cmax.

In addition, the test to reference ratio of geometric least squares means with corresponding 90% CI was within the acceptance range of 80.00 to 125.00% for ln-transformed pharmacokinetic parameter AUC0-72 for Sorafenib.

The bioequivalence of test product Sorafenib Tablets 200 mg and reference product Nexavar® tablets 200 mg of Bayer AG, Germany has formally been shown.

Safety data

Nineteen (19) adverse events (AEs) were reported by sixteen (16) subjects during the conduct of the study. Eleven (11) AEs were reported in the subjects after administration of Test Product- T and eight (08) AEs were reported in the subjects after administration of Reference Product-R. All the AEs were mild in nature.

Eight (08) subjects were withdrawn on medical grounds.

2.4.2.2. Pharmacokinetic conclusion

Based on the presented bioequivalence study the test product Sorafenib Tablets 200 mg is considered bioequivalent with reference product Nexavar® tablets 200 mg of Bayer AG, Germany.

2.4.2.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.2.4. <Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.3. Discussion on clinical aspects

One bioequivalence study was submitted for the one strength of 200 mg film-coated tablets of sorafenib applied. The study was open label, balanced, randomized, two-treatment, four-period, two-sequence, single oral dose, fully replicate, crossover, and conducted under fasting conditions in line with product-specific BE guidance for Sorafenib film-coated tablets 200 mg. The analysis was done on the parent analyte, with a validated LS-MS/MS method, according to the Guideline on bioanalytical method validation.

The acceptance criteria for Cmax were widened based on the extent of the intra-subject standard deviation of the ln-transformed value of Cmax of the reference product observed. The study confirmed high intra-subject variability of Cmax for the test and reference product. However, widened acceptance criteria were not necessary as all results fell within the conventional acceptance criteria of 80.00-125.00% for Cmax. Also, the test to reference ratio of geometric least squares means with corresponding 90% CI was within the acceptance range of 80.00 to 125.00% for ln-transformed pharmacokinetic parameter AUC0-72 for Sorafenib.

The study sites have been extensively inspected. The Applicant has discussed the critical and major findings observed in recent inspection by AEMPS, Spain in 2019 and the relevance for the submitted study. No impact has been identified to current study.

2.4.4. Conclusions on clinical aspects

The application contains an adequate review of published clinical data and the bioequivalence has formally been shown between the test product Sorafenib Tablets 200 mg and the reference product Nexavar® tablets 200 mg of Bayer AG, Germany.

2.5. Risk Management Plan

2.5.1. Safety concerns

Table 4: Summary of safety concerns

Important identified risks	• Severe skin adverse events • Reversible posterior leukoencephalopathy syndrome (RPLS) • Hemorrhage including lung hemorrhage, gastroinestinal (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 (TdP) • Pregnancy and exposure through breastfeeding
Missing information	• None

2.5.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.5.3. Risk minimisation measures

None.

2.5.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 1.1 is acceptable.

2.6. Pharmacovigilance

2.6.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.6.2. Periodic safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal

2.7. Product information

2.7.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Nexavar (EMEA/H/C/000690) and Solifenacin succinate 5/10 mg (DK/H/2339/001-002/DC). The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of sorafenib (as tosilate) 200 mg film coated tablets. The reference product Nexavar is indicated for:

Hepatocellular carcinoma

Nexavar is indicated for the treatment of hepatocellular carcinoma

Renal cell carcinoma

Nexavar 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.

Differentiated thyroid cancer

Nexavar is indicated for the treatment of patinets with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hurthle cell) thyroid carcinoma, refractory to radioactive iodine.

- However orphan drug exclusivity has been granted for follicular thyroid cancer and papillary thyroid cancer till May 27, 2024. Hence the thyroid cancer related indication was carved out from the proposed product information and this application.

No nonclinical studies have been provided for this application but an adequate summary of the available non-clinical information for the active substance was presented and considered enough. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature is considered sufficient.

The bioequivalence study forms the pivotal basis with an open label, balanced, randomized, two-treatment, four-period, two-sequence, single oral dose, fully replicate, crossover, bioequivalence study comparing two sorafenib 200 mg film-coated tablet formulations in 64 healthy adult subjects under fasting conditions. The study was conducted under standardised conditions. Sorafenib was measured in human plasma using a validated LC-MS/MS method.

The application contains adequate quality data and adequate non-clinical and clinical data and the bioequivalence has been shown.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

Having considered the data submitted in the application and available on the chosen reference medicinal product, no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendations

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Sorafenib Accord is favourable in the following indication:

Hepatocellular carcinoma

Sorafenib Accord is indicated for the treatment of hepatocellular carcinoma

Renal cell carcinoma

Sorafenib Accord 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.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription.

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.