LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Sorafenib Bluefish
(sorafenib tosilate)

SE/H/2149/01/DC

This module reflects the scientific discussion for the approval of Sorafenib Bluefish. The procedure was finalised on 2022-07-14. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Sorafenib Bluefish, 200 mg, film-coated tablet.

The active substance is sorafenib tosilate. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Sorafenib Bluefish, 200 mg, film-coated tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Bluefish Pharmaceuticals AB, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and AT, DE, IE and PT as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Nexavar, 200 mg, film-coated tablet, authorised in the EU since 2006, with Bayer AG as marketing authorisation holder.

The reference product used in the bioequivalence study is Nexavar, 200 mg, film-coated tablet, from RO with Bayer AG as marketing authorisation holder.

Potential similarity with orphan medicinal products

According to the application form and a check of the Community Register of orphan medicinal products the following 28 medicinal products have been designated as orphan medicinal products, but not yet granted a marketing authorisation in the EU:

EU Orphan Designation Number: EU/3/10/788	
EU Orphan Designation Number: EU/3/20/2285	
EU Orphan Designation Number: EU/3/15/1544	EU Orphan Designation Number: EU/3/11/872
EU Orphan Designation Number: EU/3/15/1565	EU Orphan Designation Number: EU/3/02/110
EU Orphan Designation Number: EU/3/07/477	EU Orphan Designation Number: EU/3/17/1897
EU Orphan Designation Number: EU/3/14/1378	EU Orphan Designation Number: EU/3/20/2269
EU Orphan Designation Number: EU/3/10/833	EU Orphan Designation Number: EU/3/09/700
EU Orphan Designation Number: EU/3/16/1632	EU Orphan Designation Number: EU/3/06/356
EU Orphan Designation Number: EU/3/16/1700	EU Orphan Designation Number: EU/3/02/116
EU Orphan Designation Number: EU/3/17/1902	EU Orphan Designation Number: EU/3/05/270
EU Orphan Designation Number: EU/3/05/300	EU Orphan Designation Number: EU/3/06/405
EU Orphan Designation Number: EU/3/09/686	EU Orphan Designation Number: EU/3/06/417
EU Orphan Designation Number: EU/3/05/289	EU Orphan Designation Number: EU/3/07/480
EU Orphan Designation Number: EU/3/11/890	EU Orphan Designation Number: EU/3/06/429
EU Orphan Designation Number: EU/3/11/913	EU Orphan Designation Number: EU/3/07/448

The applicant has provided a similarity report (Module 1.7.1) due to potential similarity with indications of the centrally authorised reference medicinal product chosen for this application, Nexavar, 200 mg, film-coated tablet, with Bayer AG as marketing authorisation holder.
The two applied indications which are shared with Nexavar no longer hold orphan market exclusivity:

- *renal cell carcinoma - EU/3/04/207 - orphan market exclusivity ended on 22 Jul 2016*
- *hepatocellular carcinoma - EU/3/06/364 - orphan market exclusivity ended on 01 Nov 2017*

The two indications of Nexavar (EU/1/06/342) which hold orphan market exclusivity until 27 May 2024 have been omitted by the Applicant from this application: *follicular thyroid cancer* (EU/3/13/1199) and *papillary thyroid cancer* (EU/3/13/1200).

A detailed assessment of similarity is therefore not needed at the moment.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of sorafenib are well known. As sorafenib is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Sorafenib Bluefish is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

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

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted one bioequivalence

study comparing Sorafenib, 200 mg, film-coated tablet with the reference product Nexavar, 200 mg, film-coated tablet.

Pharmacokinetic properties of the active substance
Absorption: After administration of sorafenib tablets the mean relative bioavailability is 38 - 49 % when compared to an oral solution. The absolute bioavailability is not known. Following oral administration sorafenib reaches peak plasma concentrations in approximately 3 hours. When given with a high-fat meal sorafenib absorption was reduced by 30 % compared to administration in the fasted state.
Linearity: Mean Cmax and AUC increased less than proportionally beyond doses of 400 mg administered twice daily.
Elimination: The elimination half-life of sorafenib is approximately 25 - 48 hours.

Study 19-VIN-0245
Methods
This was a single-dose, two-way crossover study conducted in 126 healthy volunteers, comparing Sorafenib, 200 mg, film-coated tablet with Nexavar, 200 mg, film-coated tablet under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of sorafenib were determined with an LC-ESI-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-72h} and C_{max}. The study was conducted between 16th August and 9th September 2019.

Results
The results from the pharmacokinetic and statistical analysis are presented in

Table 1 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for sorafenib, n=115.

Treatment	AUC_{0-72h} ** ng*h/ml	C_{max} ng/ml	t_{max} h
Test	56211 ± 29413	2314.9 ± 1134.5	4.00 (2.33 - 24.00)
Reference	59979 ± 34502	2442.2 ± 1430.7	4.00 (2.00 - 24.00)
***Ratio (90% CI)**	93.75 (86.59-101.49)	95.55 (87.92-103.84)	-
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 plasma concentration			

**calculated based on ln-transformed data **n=111*

For AUC_{0-72h} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Discussion and overall conclusion
The bioequivalence study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr). The design is in line with the product specific bioequivalence guidance (EMA/CHMP/315232/2014). The bioanalytical methods were adequately validated.

Based on the submitted bioequivalence study, Sorafenib Bluefish is considered bioequivalent with Nexavar.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

Risk Management Plan
The MAH has submitted an updated 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 Bluefish.

Safety specification
The MAH has submitted the version 1.1 RMP dated 2021-09-22 and proposed the following summary safety concerns:

Summary of safety concerns	
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 perforations • 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	• No missing information

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The submitted Risk Management Plan, version 1.1 RMP dated 2021-09-22 is considered acceptable.

The 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 RMS;
- 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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to Nexavar, EMEA/H/C/690 with regards to content and Venlafaxine Bluefish Prolonged initially approved through procedure UK/H/1400/01-03/DC. Due to Brexit, RMS is transferred to SE and current procedure number is SE/H/1870/01-03/DC.
The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Sorafenib Bluefish, is found adequate. There are no objections to approval of Sorafenib Bluefish, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The benefit/risk ratio is considered positive, and Sorafenib Bluefish, 200 mg, film-coated tablet is recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

Post approval commitments
A commitment has been made that a nitrosamine analysis and nitrosamine risk assessment update will be performed on a representative number of drug product batches once and if tablets with API sourced from Jiangsu Xidi Pharmaceuticals are manufactured.

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Sorafenib Bluefish, 200 mg, film-coated tablet was positively finalised on 2022-07-14.

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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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