LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Sunitinib Bluefish
(sunitinib)

SE/H/2245/01-03/DC

This module reflects the scientific discussion for the approval of Sunitinib Bluefish. The procedure was finalised on 2023-01-18. 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 Sunitinib Bluefish, 12,5 mg, 25 mg, 50 mg, Capsule, hard.

The active substance is sunitinib. 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 Sunitinib Bluefish, 12,5 mg, 25 mg, 50 mg, Capsule, hard. 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, PL 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 Sutent, 12.5 mg, 25 mg, 50 mg, hard capsules authorised in the Union since 2006, with Pfizer Europe MA EEIG as marketing authorisation holder.

The reference products used in the bioequivalence studies are Sutent, 50 mg, hard capsules from LV with Pfizer Limited as marketing authorisation holder and Sutent, 50 mg, hard capsules from DE with Pfizer Europe MA EEIG, as marketing authorisation holder.

Potential similarity with orphan medicinal products

Having considered the arguments presented by the applicant and with reference to Article 8 of Regulation (EC) No 141/2000, Sunitinib Bluefish is considered not similar (as defined in Article 3 of Commission Regulation (EC) No. 847/2000) to Lutathera.

Therefore, with reference to Article 8 of Regulation (EC) No. 141/2000, the existence of any market exclusivity for Lutathera in the treatment of pancreatic tumours does not prevent the granting of the marketing authorisation of Sunitinib Bluefish. This finding is without prejudice to the outcome of the scientific assessment of the marketing authorisation application.

Having considered the arguments presented by the applicant and with reference to Article 8 of Regulation (EC) No 141/2000, Sunitinib Bluefish is considered not similar (as defined in Article 3 of Commission Regulation (EC) No. 847/2000) to Onivyde.

Therefore, with reference to Article 8 of Regulation (EC) No. 141/2000, the existence of any market exclusivity for Onivyde in the treatment of pancreatic tumours does not prevent the granting of the marketing authorisation of Sunitinib Bluefish. This finding is without prejudice to the outcome of the scientific assessment of the marketing authorisation application.

Having considered the arguments presented by the applicant and with reference to Article 8 of Regulation (EC) No 141/2000, Sunitinib Bluefish is considered not similar (as defined in Article 3 of Commission Regulation (EC) No. 847/2000) to Ayvakyt.

Therefore, with reference to Article 8 of Regulation (EC) No. 141/2000, the existence of any market exclusivity for Ayvakyt in the treatment of gastrointestinal stromal tumours does not prevent the granting of the marketing authorisation of Sunitinib Bluefish. This finding is without prejudice to the outcome of the scientific assessment of the marketing authorisation application.

Having considered the arguments presented by the applicant and with reference to Article 8 of Regulation (EC) No 141/2000, Sunitinib Bluefish is considered not similar (as defined in Article 3 of Commission Regulation (EC) No. 847/2000) to Qinlock.

Therefore, with reference to Article 8 of Regulation (EC) No. 141/2000, the existence of any market exclusivity for Qinlock in the treatment of gastrointestinal stromal tumours does not prevent the granting of the marketing authorisation of Sunitinib Bluefish. This finding is without prejudice to the outcome of the scientific assessment of the marketing authorisation application.

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 sunitinib are well known. As sunitinib 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 Sunitinib 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 Sunitinib Bluefish from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics

To support the marketing authorisation application the applicant has conducted two bioequivalence studies with the 50 mg strength, one in the fasted state and one in the fed state. This is adequate since Sunitinib Bluefish capsules contain sunitinib as free base while the reference product Sutent contain sunitinib malate as active pharmaceutical ingredient. Sunitinib base is less soluble than sunitinib malate and a bioequivalence study under fed conditions is needed in addition to the fasted study to evaluate that there is no altered food effect due to the lower solubility.

Pharmacokinetic properties of the active substance

Absorption: After oral administration of sunitinib, C_{max} are generally observed from 6 to 12 hours-time to maximum concentration (t_{max}) post administration. Food has no effect on the bioavailability of sunitinib.

Linearity: In the dosing ranges of 25 to 100 mg, the area under the plasma concentration-time curve (AUC) and C_{max} of sunitinib increase proportionally with dose.

Elimination: Following oral administration in healthy volunteers, the elimination half-lives of sunitinib and its primary active desethyl metabolite are approximately 40-60 hours and 80-110 hours, respectively.

Study 19-VIN-0103 (fasted)

Methods

This was a single-dose, two-way crossover study conducted in 31 healthy volunteers, comparing Sunitinib (base), 50 mg, hard capsule with Sutent, 50 mg, hard capsule under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of sunitinib were determined with an LC-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 5th December 2019 and 6th January 2020.

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 sunitinib in fasted study 19-VIN-0103, n=31.

Treatment	AUC_{0-72h} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	1482.2 ± 338.3	41.6 ± 9.3	7.50 (5.00 - 12.00)
Reference	1479.8 ± 304.0	41.8 ± 9.2	6.50 (5.00 - 14.00)
***Ratio (90% CI)**	99.60 (96.60-102.68)	99.70 (95.22-104.39)	-
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*

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%.

Study 21-081

Methods

This was a single-dose, two-way crossover study conducted in 32 healthy volunteers, comparing Sunitinib (base), 50 mg, hard capsule with Sutent, 50 mg, hard capsule under fed conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of sunitinib were determined with an LC-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 29th October and 30th November 2021.

Results

The results from the pharmacokinetic and statistical analysis are presented in Table 2 below.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for sunitinib in fed study 21-081, n=29.

Treatment	AUC_{0-72h} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	1753.8 ± 333.7	44,9 ± 10.0	9.50 (0.00 - 14.00)
Reference	1714.7 ± 280.9	43.3 ± 8.8	9.67 (5.00 - 12.00)
***Ratio (90% CI)**	101.80 (98.09-105.64)	103.20 (99.79-106.72)	-
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*

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%.

A biowaiver was sought for the additional strengths of 12.5 and 25 mg.

Discussion and overall conclusion

The bioequivalence studies 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 bioanalytical methods were adequately validated.

Absence of studies with the additional strengths of 12.5 and 25 mg is acceptable, as all conditions for biowaiver for additional strength(s), as described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) are fulfilled and since the pharmacokinetics of sunitinib is linear between 25 mg and 100 mg.

Based on the submitted bioequivalence studies, Sunitinib Bluefish is considered bioequivalent with Sutent.

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 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 Sunitinib Bluefish.

Safety specification
The MAH has submitted the version 1.0 RMP dated 2022-01-27 and proposed the following summary of safety concerns:

Summary of safety concerns	
Important identified risks	Cardiotoxicity • Torsade de pointes • Left ventricular dysfunction/heart failure • Pericardial events • Cardiac ischemic events
	Reversible posterior leukoencephalopathy syndrome
	Hepatic failure
	Osteonecrosis of the jaw
	Severe cutaneous adverse reactions
	Renal failure
Important potential risks	Carcinogenicity
Missing information	Severe hepatic impairment

The submitted RMP is in line with the most recent RMP of the originator Sutent and is therefore considered acceptable.

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 1.0 signed 2022-01-27 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 leaflet has been performed on the basis of a bridging report making reference to Sutent, EMEA/H/C/000687 (content), and Venlafaxine Bluefish, UK/H/1400/001-003/DC (layout). 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, Sunitinib Bluefish, is found adequate. There are no objections to approval of Sunitinib 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 is considered positive, and the application is therefore 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

N/A

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

N/A

VII. APPROVAL

The decentralised procedure for Sunitinib Bluefish, 12,5 mg, 25 mg, 50 mg, Capsule, hard was positively finalised on 2023-01-18.

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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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