COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Axitinib Stada 1 mg, 3 mg, 5 mg, 7 mg, film-coated tablets (axitinib)

NL/H/5476/001-004/DC

Date: 10 July 2024

This module reflects the scientific discussion for the approval of Axitinib Stada 1 mg, 3 mg, 5 mg, 7 mg film-coated tablets. The procedure was finalised on 18 January 2023. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
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
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for 1 mg film-coated tablets 1 mg, 3 mg, 5 mg, and 7 mg film-coated tablets from Stada Arzneimittel AG

The product is indicated for: the treatment of adult patients with advanced renal cell carcinoma (RCC) after failure of prior treatment with sunitinib or a cytokine.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Inlyta 1 mg film-coated tablets, which has been registered in the EEA via a centralised procedure (EMEA/H/C/002406) by Pfizer Europe MA EEIG since 3 September 2012.

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Cyprus, Denmark, Estonia, Finland, France, Germany, Greece, Iceland, Latvia, Lithuania, Luxembourg, Norway, Romania, Spain and Sweden.

II. QUALITY ASPECTS

II.1 Introduction

Axitinib Stada are film-coated tablets and contain axitinib as active substance. The four strengths can be distinguished by the different size, shape, colour and debossing of the tablets.

Axitinib Stada 1 mg film-coated tablet is a red colour, round biconvex coated tablet, approximately 6 mm diameter and debossed with “A7TI” on one side and “1” on the other. It contains 1 mg of axitinib.

Axitinib Stada 3 mg film-coated tablet is a red colour, oval biconvex coated tablet, approximately 12 mm long by 7 mm wide and debossed with “A7TI” on one side and “3” on the other. It contains 3 mg of axitinib.

Axitinib Stada 5 mg film-coated tablet is a red colour, oval biconvex coated tablet, approximately 15 mm long by 8 mm wide and debossed with “A7TI” on one side and “5” on the other. It contains 5 mg of axitinib.

Axitinib Stada 7 mg film-coated tablet is a red colour, oval biconvex coated tablet, approximately 17 mm long by 9 mm wide and debossed with “A7TI” on one side and “7” on the other. It contains 7 mg of axitinib.

The excipients are:
Tablet core - lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate.
Film-coating - hypromellose, lactose monohydrate, titanium dioxide (E171), iron oxide red (E172), and triacetin.

The four tablet strengths are dose proportional.

The tablets are packed in oriented polyamide/aluminium/polyvinyl chloride/aluminium (oPA-Al-PVC/Al) (perforated unit) blisters.

II.2 Drug Substance

The active substance is axitinib and is not described in the European Pharmacopoeia or any other Pharmacopoeia. It is an off-white to light brown powder and has no chiral centre. Axitinib exhibits polymorphism; five crystalline anhydrous forms have been identified (I, IV, VI, XXV and XLI). When manufactured according to the manufacturing process as described in ASMF, polymorphic form IV is consistently obtained. The form supplied is polymorphic form IV. Axitinib is soluble in DMSO, slightly soluble in ethanol, and very poorly soluble in water. It is sparingly soluble in water pH 1.2 and insoluble in buffered media over pH 4.5 to 9.0.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or ‘know-how’ of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The manufacturing process consists of three steps which overall comprise five synthetic steps. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised and the manufacturing process is described in sufficient detail.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. The specifications were drawn up by the ASMF-holder, with additional requirements for particle size distribution and polymorphism. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

Stability data on the active substance have been provided for three batches in accordance with applicable European guidelines. Based on the data submitted, a retest period could be granted of 24 months when stored under the stated conditions in the ASMF. The photostability study showed that the active substance is sensitive for light.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The formulation development is based on the composition of the reference product. However, the product exhibits polymorphism and the form varies between the reference and drug product. Two pilot bioavailability studies were performed to evaluate effects of changes in the manufacturing process and composition. A description of the development of the QC dissolution method has been provided. The products used in the bioequivalence study are acceptable and the biowaiver for strengths 1 mg, 3 mg and 5 mg is acceptable. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process is considered a non-standard process due to the low amount of active substance in the drug product. The manufacturing process has been validated according to relevant European/ICH guidelines. The drug product is prepared by a wet granulation process followed by compression and film-coating. Process validation data on the product have been presented for three industrial scale batches of each strength in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with Ph.Eur. requirements, with the exception of iron oxide red, which is in accordance with Regulation EC 231/2012.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, dissolution, identification, assay, uniformity of dosage units, impurities and microbial contamination. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three industrial scale batches of each strength from the proposed production site has been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided from three industrial scale batches of the 1 mg, 5 mg, and 7 mg strength and for one industrial scale batch of the 3 mg strength stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months) in accordance with applicable

European guidelines. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. The blisters should be kept tightly closed in order to protect the tablets against moisture. All results comply with the proposed specifications and acceptance limits and no clear trends have been observed. Polymorphism was evaluated in a separate stability study whereby tablets were stored for 21 months at both long-term, intermediate and accelerated conditions. No change in polymorphism was observed. On basis of the data submitted, a shelf life was granted of 3 years. The storage conditions "Store in the original package in order to protect from moisture" are applicable.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM lactose monohydrate have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Axitinib Stada 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 Axitinib Stada is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Inlyta which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was 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

Axitinib is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The member states agreed that no further clinical studies are required, besides the one bioequivalence study with the 7 mg strength, which is discussed below.

A biowaiver is requested for the lower strengths 1 mg, 3 mg and 5 mg.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Axitinib Stada 7 mg film-coated tablets (Stada Arzneimittel AG, Germany) was compared with the pharmacokinetic profile of the reference product Inlyta 7 mg film-coated tablets (Pfizer Europe MA EEIG, Belgium).

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

Biowaiver

The following general requirements must be met where a waiver for additional strength is claimed, according to the EMA Bioequivalence guideline:

a. the pharmaceutical products are manufactured by the same manufacturing process,
b. the qualitative composition of the different strengths is the same,
c. the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule),
d. appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

The dissolution was investigated in media with pH 1.2, pH 4.5, pH 6.8 and QC media, according to the EMA Bioequivalence guideline. The manufacturing process of axitinib 1 mg, 3 mg , 5 mg, 7 mg film-coated tablets is the same and the ratio of excipients to the amount of active substance is the same for all strengths. Further, a comparable *in vitro* dissolution profile was shown (dissolution of >85%) for the different strength tablets under the pH 1.2 condition. No drug dissolution was observed under the pH 6.8 condition. Therefore calculation of the F2 statistic is not required. Minimal dissolution was observed under the pH 4.5 condition.

Dissolution of all strengths at pH 4.5 is low (≤2.9%). Trends are the same for all strengths and *in vitro* dissolution is therefore considered acceptable.

Bioequivalence studies

Design

A single-dose, randomised, four-period, two-treatment, two-sequence, crossover, open label, balanced bioequivalence study was carried out under fasted conditions in 179 healthy male/female subjects, aged 20-53 years. Each subject received a single dose (7 mg) of one of the two axitinib formulations. The tablet was orally administered with 240 mL water after 10 hours overnight fasting. There were four dosing periods, separated by a washout period of 4 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24 and 32 hours after administration of the products.

The design of the study is acceptable. Axitinib may be administered with or without food.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

179 subjects enrolled in the study. Three subjects withdrew from the study after period I: two subjects did not report to the clinical facility and one due to an adverse effect. Five subjects did not report to the clinical facility in one period during the study. Two subjects were positive for protocol deviation in period 4 and withdrawn. One subject experienced an adverse event (body ache) after dosing in period 3 (and dropped out of period 3 only) and one subject experienced an adverse effect before dosing in period 4 (and dropped out of period 4 only). Adverse events experienced during the study included shoulder pain, headache and body ache. 167 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of axitinib, 7 mg under fasted conditions.

Treatment N=167	**AUC_{0-t}** (ng.h/mL)	**$AUC_{0-\infty}$** (ng.h/mL)	**C_{max}** (ng/mL)	**t_{max}** (h)
Test	211.2 ± 178.6	215.1 ± 179.4	59.6 ± 41.6	1.5 (0.5 – 5.0)
Reference	173.9 ± 132.1	178.1 ± 131.9	46.2 ± 30.5	1.5 (0.50 – 4.0)
***Ratio (90% CI)**	1.07 (0.98 – 1.18)	-	1.18 (1.08 – 1.30)	-

$AUC_{0-\infty}$	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 = last measurable concentration
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**In-transformed values*

Conclusion on bioequivalence stud:
Potential bioequivalence has been studied between a single dose Axitinib Sandoz 7 mg film-coated tablets and Inlyta 7 mg film-coated tablets under fasting conditions in a replicate design study. The point estimates (90% CIs) for the AUC_{0-t} and Cmax ratios for the test and reference product comparison were within the acceptance range of 80.00 – 125.00% for AUC_{0-t} and the widened acceptance range of 69.84% - 143.19% for Cmax. Widening of the acceptance range for Cmax is in line with requirements in the BE guideline. Observed ratios (90% CI) for AUC_{0-t} and Cmax were 107.4 (98.0 - 117.7) and 118.5 (107.8 –130.3), respectively. Based on the submitted bioequivalence study Axitinib Stada 7 mg is considered bioequivalent with Inlyta 7 mg.

In addition, based on the manufacturing procedure, tablet composition and comparative dissolution data, a biowaiver for the additional strength Axitinib Stada 1 mg, 3 mg and 5 mg film-coated tablet, referring to the demonstrated BE for the 7 mg strength, was granted.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Axitinib Stada.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	• Arterial embolic and thrombotic events • Congestive heart failure/cardiomyopathy • Effects on the exocrine pancreas • Gastrointestinal perforation and fistula • Haemorrhage • Posterior reversible encephalopathy syndrome • Renal failure • Venous embolic and thrombotic events
Important potential risks	• Carcinogenicity

	• Osteonecrosis of jaw • Reproductive and developmental toxicity • Torsade de pointes due to QT prolongation
Missing information	• Risks in paediatric subjects • Risks in pregnant and lactating women • Risks in subjects with a recent major surgery (within 4 weeks) or radiation therapy (within 2 weeks) • Risks in subjects with active peptic ulcer disease • Risks in subjects with brain metastasis, spinal cord compression, or carcinomatous meningitis • Risks in subjects with moderate and severe renal impairment (serum creatinine >1.5 times the ULN or calculated creatinine clearance <60 mL/min) • Risks in subjects with severe hepatic impairment (Child-Pugh Class C)

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 Inlyta. 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

The package leaflet (PL) has been evaluated via two user consultation studies in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was English.

The first full user testing report to justify that the lay-out and design (house style) of the patient leaflet of the current applications, which is from the same MAHa, is readable. The test consisted of: a pilot test with two participants, followed by two rounds with 10 participants each.

The second user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Inlyta, EU/1/12/777. The

bridging report submitted by the MAH has been found acceptable; bridging is justified for content of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Axitinib Stada 1 mg, 3 mg, 5 mg, 7 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Inlyta 1 mg film-coated tablets. Inlyta 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 Axitinib Stada with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 18 January 2023.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/5476/001-4/IA/001	**Type IA: B.II.b.2.a** *Change to importer, batch release arrangements and quality control testing of the finished product* • *Replacement or addition of a site where batch control/testing takes place*	No	09-10-2023	Approved	N/A