COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

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

NL/H/5644/001-004/DC

Date: 8 October 2025

This module reflects the scientific discussion for the approval of Axitinib Teva 1 mg, 3 mg, 5 mg and 7 mg, film-coated tablets. The procedure was finalised on 13 May 2024. 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
AE	Adverse Event
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
RCC	Renal Cell Carcinoma
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 Axitinib Teva 1 mg, 3 mg, 5 mg and 7 mg, film-coated tablets, from Teva GmbH.

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 by Pfizer Europe MA EEIG in the European Union since 3 September 2012 (EMEA/H/C/002406).

The concerned member states (CMS) involved in this procedure were:

- NL/H/5644/001/DC (1 mg strength) and NL/H/5644/001/DC (5 mg strength): Austria, Belgium, Bulgaria, Croatia, Denmark, Germany, Greece, France, Italy, Luxembourg, Norway, Portugal, Slovenia, Spain and Sweden.
- NL/H/5644/002/DC (3 mg strength) and NL/H/5644/004/DC (7 mg strength): Austria, Belgium, Denmark, Germany, France, Italy, Luxembourg, Norway and Sweden.

II. QUALITY ASPECTS

II.1 Introduction

Axitinib Teva are film-coated tablets. Each tablet contains, depending on the strength, 1 mg, 3 mg, 5 mg or 7 mg of the active substance axitinib.

The 1 mg strength is a red coloured, round biconvex coated tablet, approximately 6 mm diameter and debossed with “A7TI” on one side and “1” on the other.
The 3 mg strength is a red coloured, oval biconvex coated tablet, approximately 12 mm long by 7 mm wide and debossed with “A7TI” on one side and “3” on the other.
The 5 mg strength is a red coloured, oval biconvex coated tablet, approximately 15 mm long by 8 mm wide and debossed with “A7TI” on one side and “5” on the other.
The 7 mg strength is a red coloured, oval biconvex coated tablet, approximately 17 mm long by 9 mm wide and debossed with “A7TI” on one side and “7” on the other.

The excipients are:
Tablet core – microcrystalline cellulose, lactose monohydrate, croscarmellose sodium and magnesium stearate.
Tablet film-coating – hypromellose, titanium dioxide (E171), lactose monohydrate, triacetin (E1518) and iron oxide red (E172).

The four tablet strengths are dose proportional.

The tablets are packed in oriented polyamide/polyvinyl chloride (OPA/PVC)- aluminium blister packs. The excipients and packaging are usual for this type of dosage form.

II.2 Drug Substance

Axitinib is an established active substance not described in the European Pharmacopeia or Pharmacopeia of any member state. It is an off-white to light brown powder. Axitinib is soluble in dimethyl sulfoxide, slightly soluble in ethanol and very poorly soluble in water. It is sparingly soluble in water pH 1.2 and practically insoluble in buffered media over pH 4.5 to 9.0. The drug substance is light sensitive. Axitinib has no chiral center. Axitinib shows polymorphism. For this product, polymorphic form IV is consistently produced.

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 is described in 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. Impurities have been discussed in sufficient detail.

Quality control of drug substance
The active substance specification is considered adequate to control the quality, with additional requirements for particle size distribution and polymorphism. Batch analytical data demonstrating compliance with this specification have been provided for three production scale 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.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained.

The formulation development is based on the composition of the reference product. However, Axitinib exhibits polymorphism and, whereas form XLI is used in the reference product, form IV is used in the generic 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 quality control 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 drug product is prepared by a wet granulation process followed by compression and film-coating. The various steps of the manufacturing process, the process parameters and the in-process controls have been adequately described. The manufacturing process has been adequately validated according to relevant European guidelines.

Process validation data on the product has been presented for three industrial scale batches of each strength.

Control of excipient

The excipients comply with Ph.Eur. requirements, with the exception of iron oxide red, which is in accordance with Regulation EC 231/2012. The relevant functionality-related characteristics are included in the excipient specifications. These specifications are acceptable.

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 quality. 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 on three industrial scale batches of each strength from the proposed production sites have been provided, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product have been provided for three production scaled batches of the 1 mg, 5 mg and 7 mg strength and for one production scaled 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. On basis of the data submitted, a shelf life was granted of 3 years. The labelled storage conditions are 'Store in the original blisters in order to protect from moisture' and 'This medicinal product does not require any special temperature storage conditions'.

No specific storage conditions needed to be included in the SmPC or on the label.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Scientific data and/or certificates of suitability issued by the EDQM for 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 Teva 1 mg, 3 mg, 5 mg and 7 mg has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Axitinib Teva 1 mg, 3 mg, 5 mg and 7 mg, 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 Teva 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 one bioequivalence study for the 7 mg strength, which is discussed below. In addition, a biowaiver was 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 7 mg, film-coated tablets (Teva GmbH, Germany) was compared with the pharmacokinetic profile of the reference product Inlyta 7 mg film-coated tablets (Pfizer Manufacturing Deutschland GmbH, Germany).

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 were met for the waiver for additional strength, according to the EMA Bioequivalence guideline:

a. All strengths are manufactured by the same process.
b. The qualitative composition of the different strengths is the same.
c. The composition of the strengths is 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.

The dissolution was investigated according to the EMA Bioequivalence guideline. The calculated f_2 similarity factor values for the 1 mg, 3 mg and 5 mg strengths, each of them compared to the 7 mg strength at three pH values (pH 1.2, pH 4.5 and pH 6.8), were within criteria (>50%). An f_2 value between 50 and 100% suggests that the dissolution profiles of the two compared dissolution profiles are similar.

Overall, the biowaiver of strengths is acceptable.

Bioequivalence studies

Design

A single-dose, randomised, four-period, two-treatment, two-sequence, full replicate crossover bioequivalence study was carried out under fasted conditions in 179 healthy male

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 an overnight fast of at least 10 hours. There were four dosing periods, separated by a washout period of four 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 taken without reference to food intake. From the literature it is known that food does not interact with the absorption of axitinib. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

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
A total of 179 subjects were enrolled in the study, 167 subjects completed all the periods of the study as per protocol. Two subjects did not report to the clinical facility after period 1, five other subjects did not report to the clinical facility in one period during the study. Two subjects were positive for drugs abuse in period 4 and were withdrawn from period 4. One subject was withdrawn from the study due to an adverse event (AE) after period 1. One subject experienced an AE before dosing in period 4 (and dropped out of period 4 only). One subject experienced an AE after dosing in period 3 (and dropped out of period 3 only).
Pharmacokinetic analysis was performed of plasma concentrations of all 179 subjects.

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

Treatment N=179	**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)
Reference	173.9 ± 132.1	178.1 ± 131.9	46.2 ± 30.5	1.5 (0.5 – 4)
***Ratio (90% CI)**	1.09 (0.99-1.20)-	-	1.19 (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 = 36 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Conclusion on bioequivalence study:
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Axitinib Teva 7 mg, film-coated tablets is considered bioequivalent with Inlyta 7 mg film-coated tablets.

The results of the BE study with the 7 mg formulation can be extrapolated to the lower strengths 1 mg, 3 mg and 5 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

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 Teva. At the time of approval, the most recent version of the RMP was version 1.1 dated 19 December 2023.

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

Important identified risks	• Arterial embolic and thrombotic events • Gastrointestinal perforation and fistula • Haemorrhage • Posterior reversible encephalopathy syndrome • Venous embolic and thrombotic event • Effects on the exocrine pancreas • Renal failure • Congestive heart failure/cardiomyopathy
Important potential risks	• Torsade de pointes due to QT prolongation • Reproductive and developmental toxicity • Carcinogenicity • Osteonecrosis of the jaw
Missing information	• Risks in pregnant and lactating women • Risks in paediatric subjects • Risks in subjects with moderate and severe renal impairment (serum creatinine >1.5 times the upper limit normal (ULN) or calculated creatinine clearance <60 ml/min) • Risks in subjects with severe hepatic impairment (Child-Pugh Class C) • Risks in subjects with brain metastasis, spinal cord compression, or carcinomatous meningitis • Risks in subjects with active peptic ulcer disease • Risks in subjects with a recent major surgery (within 4 weeks) or radiation therapy (within 2 weeks)

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. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a double bridge approach. The bridging report is making reference to Inlyta 1 mg, 3 mg, 5 mg and 7 mg film-coated tablets, EU/1/12/777/001-012, for the content. As for the design and layout, reference is made to Oxycodone Hydrochloride 10 mg, 20 mg, 40 mg and 80 mg prolonged-release tablets, developed by Teva.
The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Axitinib Teva 1 mg, 3 mg, 5 mg and 7 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Inlyta 1 mg, 3 mg, 5 mg and 7 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 Teva with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on **13 May 2024**.

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/5644/001 -004/II/001	Other variation: - Submission of the most recent version of the ASMF	No	25-9-2024	Approved	N.A.