COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Gefitinib Teva 250 mg film-coated tablets

(gefitinib)

NL/H/4152/001/DC

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This module reflects the scientific discussion for the approval of Gefitinib Teva 250 mg film-coated tablets. The procedure was finalised at 5 October 2018. 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
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
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 Gefitinib Teva 250 mg film-coated tablets from Teva B.V.

The product is indicated as monotherapy for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating mutations of EGFR-TK (see SmPC section 4.4).

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Iressa 250 mg film-coated tablets (EU/1/09/526) which has been registered in the EEA by AstraZeneca AB since 24 June 2009.

The concerned member states (CMS) involved in this procedure were Belgium, Bulgaria, Germany, Denmark, Estonia, Spain, Finland, France, Croatia, Hungary, Italy, Lithuania, Latvia, Luxembourg, Portugal, Slovakia and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Gefitinib Teva is a brown, round, convex film-coated tablet, debossed with “250” on one side and plain on the other. Each tablet contains as active substance 250 mg of gefitinib.

The film-coated tablets are packed in OPA/Alu/PVC/Alu blisters.

The excipients are:
Tablet core - lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, sodium laurilsulphate, povidone and magnesium stearate.
Tablet coating - Opadry II Brown 85F165081: poly(vinyl alcohol), macrogol 3350, talc, iron oxide yellow, iron oxide red and titanium dioxide.

II.2 Drug Substance

The active substance is gefitinib, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white, crystalline powder

and is practically insoluble in water. The compound does not contain a chiral centre and therefore stereochemistry is not an issue. The polymorphic form of gefitinib in the formulation is crystalline Form 1

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 drug substance is manufactured in four synthetic steps and two purification steps. No class I solvents are used. The final drug substance is micronized. The active substance was adequately characterised. The specifications for the starting materials and intermediate are acceptable.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. It includes additional requirements for residual solvents, polymorphic form and particle size. Batch analytical data demonstrating compliance with this specification have been provided for five full scale batches.

Stability of drug substance

Stability data has been provided for six batches stored at 25°C/60% RH (three pilot-scale batches for 36 months, two scale-up batches for 24 months, one commercial-scale batch for 12 months) and 40°C/75% RH (six batches for 6 months). No clear up- or downward trends are observed for any of the batches, under long-term or accelerated conditions. Based on the data submitted, a retest period could be granted of 36 months, for which no special storage conditions are required. However, the proposed storage condition "Preserve in well closed containers between 20°C and 25°C (excursions are allowed between 15°C and 30°C). Store protected from light and moisture" is acceptable.

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.

Three bioequivalence studies have been performed, in which the bioequivalence of complete and dispersed tablets was assessed. The biobatch was manufactured according to the finalised composition and manufacturing process and is a representative batch.

Dissolution profiles of the test and reference product in media with pH 1.2, pH 4.5, pH 6.8 have been provided. Similarity between the profiles of the test and reference product has been shown. The discriminatory power of the dissolution method has been demonstrated. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The main steps of the manufacturing process are wet granulation, blending, compression and film-coating. The tablets are manufactured with a standard process. The manufacturing process has been adequately validated according to the relevant European guidelines. Process validation data on the product has been presented for three full scaled batches in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with Ph.Eur. requirements or Regulation EC 231/2012 requirements and relevant functionality-related characteristics are controlled. 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 description, identification, assay, dissolution, uniformity of dosage units, water content, related substances and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three pilot scaled and three full scaled batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability study results have been provided for three full scaled batches stored at 25°C/60% RH (6 months) and 40°C/75% RH (6 months) as well as on three supportive, pilot scaled batches stored at 25°C/60% RH (24 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). Out of specification results for dissolution were seen after three months storage at accelerated conditions for the supportive batches, without any significant changes or trends observed in the other tested parameters and storage conditions. No clear changes or trends were observed in the full scaled stability batches at both storage conditions. On basis of the data submitted, a shelf life was granted of 27 months. This medicinal product does not require any special storage conditions.

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

Scientific data and/or certificates of suitability issued by the EDQM 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 Gefitinib Teva 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 Gefitinib Teva is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Iressa which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. 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. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Gefitinib is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted three bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

Bioequivalence studies

The MAH conducted three bioequivalence studies in which the pharmacokinetic profile of the test product Gefitinib Teva 250 mg film-coated tablets (Teva B.V., The Netherlands) is compared with the pharmacokinetic profile of the reference product Iressa 250 mg film-coated tablets (AstraZeneca, Sweden/Germany):

- Study 3576/14: single dose bioequivalence study under fasting conditions.
- Study BE-1834-17: single dose bioequivalence study under fasting conditions, using a larger batch size for the test formulation.
- Study BE-1835-17: single dose bioequivalence study under fasting conditions administered as a dispersion.

The choice of the reference product in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

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.

Study 3576/14

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 48 healthy male subjects, aged 19-43 years. Each subject received a single dose (250 mg) of one of the two gefitinib formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were two dosing periods, separated by a washout period of 14 days.

Blood samples were collected pre-dose and at 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 10, 12, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable. A single dose, crossover study to assess bioequivalence is considered adequate. According to the SmPC, the tablet may be taken with or without food. As such, the fasting conditions applied in the study are considered adequate.

Results

Two subjects were withdrawn due to adverse events before dosing in Period II. Two subjects did not check in for Period II. Therefore, 44 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=44	AUC_{0-t} (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	5429 ± 1586**	207 ± 65[#]	4.75 (2.0 – 36.0)[#]
Reference	3904 ± 1637**	154 ± 60[#]	6.25 (4.0 – 12.0)[#]
***Ratio (90% CI)**	1.00 (0.95 – 1.05)	1.04 (0.98 – 1.10)	--
CV (%)	12.3	16.1	--

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 concentration
CV coefficient of variation

**ln-transformed values*
***n=42*
[#]n=44

Study BE-1834-17

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 44 healthy male subjects, aged 19-43 years. Each subject received a single dose (250 mg) of one of the two gefitinib formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were two dosing periods, separated by a washout period of 14 days.

Blood samples were collected pre-dose and at 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 10, 12, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable. A single dose, crossover study to assess bioequivalence is considered adequate. According to the SmPC, the tablet may be taken with or without food. As such, the fasting conditions applied in the study are considered adequate.

Results

Four subjects did not report to the facility for Period II check in. Two subjects were withdrawn due to adverse event before dosing in Period II. Therefore, 38 subjects were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of gefitinib under fasted conditions.

Treatment N=28	AUC_{0-t} (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	5537 ± 2198	208 ± 80	5.0 (3.0 – 10.0)
Reference	5454 ± 1937	200 ± 73	5.0 (2.5 – 12.0)
***Ratio (90% CI)**	0.99 (0.93 – 1.05)	1.01 (0.91 – 1.12)	--
CV (%)	16.5	26.9	--

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 concentration
CV coefficient of variation

**ln-transformed values*

Study BE-1835-17

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 44 healthy male subjects, aged 19-40 years. Each subject received a single dose (250 mg) of one of the two gefitinib formulations after an overnight fast. The tablets were dropped into half a glass of (non-carbonated) water (120 ml), without crushing, and the glass stirred until the tablet had dispersed (approximately 15 minutes) and the contents subsequently drunk immediately. The glass was rinsed with a further half glass of water (120 ml) and the contents drunk. There were two dosing periods, separated by a washout period of 14 days.

Blood samples were collected pre-dose and at 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 10, 12, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable. A single dose, crossover study to assess bioequivalence is considered adequate. According to the SmPC, the tablet may be taken with or without food. As such, the fasting conditions applied in the study are considered adequate.

Results

One subject withdrew consent on his own accord from the study before dosing in Period I, one subject did not report to the facility for Period II check in, one subject was found breath alcohol test positive during Period II check in, and one subject was found drug of abuse test positive during Period II check-in. Therefore, 40 subjects were eligible for pharmacokinetic analysis.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of gefitinib under fasted conditions.

Treatment N=40	AUC_{0-t} (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	5719 ± 1532	223 ± 59	4.5 (4.0 – 7.0)
Reference	5759 ± 1521	231 ± 69	5.0 (2.0 – 7.0)
***Ratio (90% CI)**	1.00 (0.96 – 1.04)	0.98 (0.92 – 1.04)	--
CV (%)	10.2	16.9	--

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 concentration
CV coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence studies

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Gefitinib Teva 250 mg film-coated tablets is considered bioequivalent with Iressa 250 mg film-coated tablets. In addition, bioequivalence has been shown between the 250 product to be marketed and the 250 mg reference product, both administered after dispersion of the tablet.

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 Gefitinib Teva.

Table 4. Summary table of safety concerns as approved in RMP

Important identified risks	• Interstitial lung disease • Hepatitis • Gastrointestinal perforation • Drug-drug interactions: interactions with inducers and inhibitors of CYP3A4 isoenzyme; interactions

	mediated by CYP2D6 isoenzyme; interactions with medicines that cause significant sustained elevations of gastric pH
Important potential risks	• Haemorrhage events (including gastrointestinal haemorrhage and tumour haemorrhage) • Cerebrovascular events • Drug interactions: interactions with oral anticoagulants
Missing information	• Use in regnant or lactating women • Use in patients with severe renal impairment

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 Iressa. 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

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Iressa 250 mg film-coated tablets. 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

Gefitinib Teva 250 mg film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Iressa 250 mg film-coated tablets. Iressa 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 Gefitinib Teva with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 5 October 2018.

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