COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Gefitinib Sandoz 250 mg, film-coated tablets

(gefitinib)

NL/H/4128/001/DC

Date: 29 November 2018

This module reflects the scientific discussion for the approval of Gefitinib Sandoz 250 mg, film-coated tablets. The procedure was finalised at 18 July 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

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
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 Sandoz 250 mg, film-coated tablets from Sandoz 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 Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Germany, Estonia, Spain, France, Croatia, Hungary, Italy, Lithuania, Latvia, Poland, Romania, 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 Sandoz is a brown, round, biconvex film-coated tablet, impressed with “250” on one side and plain on the other side and contains as active substance 250 mg of gefitinib.

The film-coated tablets are packed in in aluminium-OPA/Alu/PVC perforated unidose blisters or aluminium-OPA/Alu/PVC non-perforated blisters.

The excipients are:
Tablet core - lactose monohydrate, microcrystalline cellulose (E460), croscarmellose sodium (E468), povidone K30 (E1201), magnesium stearate (E470b), sodium laurilsulfate.
Tablet coating - polyvinyl alcohol (E1203), macrogol 3350 (E1521), talc (E553b), titanium dioxide (E171), iron oxide red (E172), iron oxide yellow (E172).

II.2 Drug Substance

The active substance is gefitinib, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Gefitinib is a white or almost white crystalline powder. It is practically insoluble in water, slightly soluble in anhydrous ethanol, and practically insoluble in heptane. Gefitinib exhibits polymorphism; the product produced by the MAH is form-1.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for sufficient batches.

Stability of drug substance
The active substance is stable for two years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

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.

A bioequivalence study has been performed using a test batch. Dissolution profiles of test and reference product (Iressa) batches in 900 ml media with pH 1.2, pH 4.5, pH 6.8. Similarity of the profiles has been shown.

Manufacturing process
The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three batches in accordance with the relevant European guidelines.

Control of excipients
The excipients used are in compliance with relevant Ph.Eur. monographs or Regulation EC 231/2012 requirements. 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, identification, identification of iron oxides and titanium dioxide, diameter, assay, dissolution, uniformity of dosage units, related substances, water content and microbial examination. 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 batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability study results have been provided on three batches at long-term conditions (12 months) and accelerated conditions (6 months). The product was packaged in the proposed commercial packaging. The results are within proposed specification limits. The product is considered photostable. No significant changes are observed during the updated long-term stability studies. On basis of the data submitted, a shelf life was granted of 24 months. This medicinal product does not require any special temperature storage conditions and should be stored in the original container in order to protect from moisture.

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 Sandoz 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 Sandoz 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 one pivotal bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Gefitinib Sandoz 250 mg, film-coated tablets (Sandoz B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Iressa 250 mg film-coated tablets (AstraZeneca AB, Sweden).

A pilot study was conducted with the same design with less subjects. Considering that the power has been increased, the pivotal study will prevail. No pooling data from the two studies is found necessary.

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.

Bioequivalence study

Design

An open-label, randomized, two-treatment, four-period, two-sequence, single dose, replicate, crossover bioequivalence study was carried out under fasted conditions in 40 healthy male subjects, aged 46 ± 13 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 a fasting period. There were four dosing periods, separated by a washout period of 14 days.

Blood samples were collected pre-dose and at 1, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 9, 10, 14, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable. The wash-out period of 14 days is considered adequate to avoid carry-over effects. The sampling scheme is considered appropriate.

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

Seven subjects were withdrawn from the study. The reasons for withdrawing the subjects are acceptable and were pre-defined in the study protocol. A total of 33 subjects completed all four periods, in which all 40 subjects had at least one Test treatment, and 39 subjects had at least one Reference treatment. Samples from 39 subjects were analysed and considered in the statistical analysis.

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

Treatment N=39	**AUC_{0-t} (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	3996 ± 1531	144 ± 63	5.5 (2.0 - 10)
Reference	3828 ± 1488	138 ± 60	5.25 (2.0 - 36.1)
***Ratio (90% CI)**	1.04 (1.00 - 1.10)	1.06 (0.98 - 1.14)	--
CV (%)	16.8	27.3	--

$AUC_{0-\infty}$	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 hours
C_{max}	maximum plasma concentration
t_{max}	time for maximum concentration
$t_{1/2}$	half-life
CV	coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence study

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 study Gefitinib Sandoz 250 mg is considered bioequivalent with Iressa 250 mg.

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 Sandoz.

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

Important identified risks	• Interstitial lung disease (ILD) • 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-drug interactions: interactions with oral anticoagulants
Missing information	• Use in pregnant 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. 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 Sandoz 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 Sandoz with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 18 July 2017.

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