COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Gefitinib Glenmark 250 mg film-coated tablets

(gefitinib)

NL/H/4111/001/DC

Date: 29 November 2018

This module reflects the scientific discussion for the approval of Gefitinib Glenmark 250 mg film-coated tablets. The procedure was finalised at 14 August 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 Glenmark 250 mg film-coated tablets, from Glenmark Arzneimittel GmbH.

The product is indicated for 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.

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 which has been registered in the EEA by AstraZeneca AB (Gärtunavägen) since 24 May 2009 via a centralised procedure. (EU/1/09/526/001)

The concerned member states (CMS) involved in this procedure were Czech Republic, Germany, Denmark, Poland, Romania, Sweden 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 Glenmark is a brown, round and biconvex film-coated tablet marked with “250” on one side and plain on the other. Each tablet contains 250 mg of gefitinib.

The film-coated tablets are packed in PVC/PVDC-Aluminium perforated or non-perforated blisters. Additionally, the blisters may be packed into aluminium pouches.

The excipients are:
Tablet core - lactose monohydrate, microcrystalline cellulose, crospovidone, povidone, sodium laurilsulfate and magnesium stearate.
Tablet coating - polyvinyl alcohol, macrogol, talc, titanium dioxide (E171), red iron oxide (E172) and yellow iron oxide (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 to almost white crystalline powder and practically insoluble in water and in heptane, slightly soluble in methanol and anhydrous ethanol and freely soluble in dimethylsulfoxide. The substance exhibits polymorphism and the for this product Form 1 anhydrous is used.

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 and meets the requirements of the monograph in the Ph.Eur.

Stability of drug substance
The active substance is stable for 2 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 are explained. A bioequivalence study is performed between the test product and the reference product Iressa. The dissolution profiles generated during manufacturing of the registration batches comply with the requirements stated in the Guideline on the investigation of bioequivalence. The exemption of a single data set is considered acceptable based on the provided rationale. Besides, two suitable alternative statistical methods prove the similarity of dissolution profiles between test and reference product. Analytical validation data and dissolution data of batches used in the bioequivalence study demonstrate that the proposed test method is precise and accurate at the specified time point. The proposed test method is therefore considered fit for purpose to support setting of specifications for quality control and to control the batch-to-batch consistency.

Manufacturing process

The manufacturing process has been validated according to relevant European guidelines. The process consists of blending, granulation, drying, sieving, blending, tablet compression , film-coating and packaging. Process validation data on the product have been presented for three batches in accordance with the relevant European guidelines.

Control of excipients

All excipients except the coating agent Opadry meet the requirements of the Ph. Eur. The colouring ingredients included in the film-coating comply with the applicable Commision Regulation (EU). The 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, diameter, assay, dissolution, uniformity of dosage units, related substances, 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 four batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for four batches stored at 25°C/60% RH (for unpouched blisters: 3 batches 24 months, 1 batch 9 month; for pouched blisters 3 batches 18 months, and 1 batch 6 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). The product was packaged in the proposed commercial packaging of PVC/PVDC-Alu blisters. The blisters may be packed into aluminium pouches. In accelerated storage conditions out of specification results were obtained for both, pouched and unpouched samples, at 6 months testing point. Accordingly, a storage claim is proposed “Do not store above 30°C”. The available stability results at intermediate and long-term storage conditions are well within the applied acceptance criteria. Based on the stability results provided the claimed shelf-life of 24 months can be accepted. The product appears to be photostable.

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

Lactose monohydrate is the only excipients of animal origin. The milk used for the manufacturing of lactose monohydrate is stated to be sourced from healthy animals in the same conditions as milk is collected for human consumption. During the production process, besides whey from cow´s milk and calf rennet, no other ruminant materials are used.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Gefitinib Glenmark 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 Glenmark 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 a 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 Glenmark 250 mg film-coated tablets (Glenmark Arzneimittel GmbH, Germany) is compared with the pharmacokinetic profile of the reference product Iressa 250 mg film-coated tablets (AstraZeneca AB (Gärtunavägen), Sweden).

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

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 48 (41 healthy males and 7 female) subjects, aged 19-55 years. Each subject received a single dose (250 mg) of one of the 2 gefitinib formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were 2 dosing periods, separated by a washout period of 21 days.

Blood samples were collected pre-dose and at 0.5, 1, 2, 3, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 10, 12, 16, 24, 36, 48 and 72 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 is considered adequate.

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

Four subject were withdrawn from the study due to personal reasons, medical issues (not related to the study) or substance abuse. 44 subjects completed the study and 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_{0-72h}** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)
Test	3786 ± 1653	158 ± 73	6.25 (3.0-10.0)
Reference	3904 ± 1637	154 ± 60	6.25 (4.0-12.0)
***Ratio (90% CI)**	0.96 (0.92 – 1.01)	0.99 (0.91 – 1.08)	--
CV (%)	14.2	23.1	--

AUC_{0-72} area under the plasma concentration-time curve from time zero to 72 hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
CV coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-72h} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Gefitinib Glenmark is considered bioequivalent with Iressa.

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 Glenmark.

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

Important identified risks	• ILD (Interstitial Lung Disease • Hepatitis • Gastrointestinal perforation • Drug-drug interactions: interactions with inducers and inhibitor 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 patient 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

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of: a pilot test with 2 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Gefitinib Glenmark 250 mg film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of product 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 Glenmark with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 14 August 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