COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Gefitinib Synthon 250 mg, film-coated tablets

(gefitinib)

NL/H/4098/001/DC

Date: 23 November 2018

This module reflects the scientific discussion for the approval of Gefitinib Synthon 250 mg, film-coated tablets. The procedure was finalised at 11 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
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 Synthon 250 mg, film-coated tablets from Synthon BV.

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 section SmPC 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 state (CMS) involved in this procedure was Luxembourg.

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

II. QUALITY ASPECTS

II.1 Introduction

Gefitinib Synthon is a brown coloured, round biconvex film-coated tablet, debossed with G9FB 250 on one side and contains as active substance 250 mg of gefitinib.

The film-coated tablet is packed in oPA/Al/PVC-Al perforated or non-perforated blister.

The excipients are:
Tablet core - sodium laurilsulfate, lactose monohydrate, cellulose microcrystalline, povidone, croscarmellose sodium and magnesium stearate.
Tablet coating - polyvinyl alcohol, macrogol, talc, iron oxide red (E172), iron oxide yellow (E172) and iron oxide black (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 crystalline powder, which is presented as plate-like crystals. The solubility of gefitinib in aqueous solution is pH dependant. At pH 3 it is sparingly soluble, while it is practically insoluble at pH 7. Gefitinib free base form I is used. A

justification for the absence of a test for polymorphic form and for microbial purity is provided.

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. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
The active substance is stable for 36 months 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. The MAH has identified the Quality Target Product Profile and Critical Quality Attributes (CQA). Formulation development and manufacturing process development has been performed in view of these CQAs.

A bioequivalence study has been performed using a test batch. Dissolution profiles of test and reference product (Iressa) batches in media with pH 1.2, pH 4.5, pH 6.8, pH 6.8 and 5% tween, and the QC medium (water and 5% tween) have been provided. Similarity of the profiles has been shown except at pH 4.5. The discrepancy has been adequately addressed.

Manufacturing process
The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for sufficient 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, assay, dissolution, uniformity of dosage units and impurities. 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 (24 months) and accelerated conditions (6 months). The product was packaged in the proposed packaging. The results are within proposed specification limits. The product is considered photostable. On basis of the data submitted, a shelf life was granted of 36 months. The product is not sensitive to moisture or light. No specific storage restriction needs to be applied.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose is manufactured from milk which is sourced from healthy animals in the same conditions as milk collected for human consumption, and lactose is prepared without the use of other ruminant materials than milk and calf rennet. Magnesium stearate is of vegetable origin.
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 Synthon 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 Synthon 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 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 Synthon 250 mg, film-coated tablets is compared with the pharmacokinetic profile of the reference product Iressa 250 mg film-coated tablets (AstraZeneca, Lithuania).

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 studies

Design

A single dose, open label, randomised, two-treatment, two-sequence, two-period, crossover, oral bioequivalence study was carried out under fasted conditions in 60 healthy (56 male/4 female subjects, aged 19-55 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 0.5, 1, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 9, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable.

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

One subject was withdrawn from the study before dosing of Period II for safety reasons (ocular hyperaemia of mild severity). Therefore, 59 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=59	**AUC_{0-t} (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**	**$t_{1/2}$ (h)**
Test	3759 ± 1568	147 ± 67	6.0 (3.5 – 36.0)	23 ± 5
Reference	3708 ± 1643	143 ± 72	6.5 (3.0 – 36.0)	24 ± 6
***Ratio (90% CI)**	1.02 (0.97 – 1.08)	1.04 (0.96 – 1.13)	--	--
CV (%)	17.7	28.1	--	--

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
$t_{1/2}$ 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 Synthon 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 Synthon.

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

Important identified risks	• 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 • Gastrointestinal perforation • Hepatitis • Interstitial lung disease (ILD)
Important potential risks	• Cerebrovascular events • Drug-drug interactions: • Interactions with oral anticoagulants • Haemorrhage events
Missing information	• Use in patients with severe renal impairment • Use in pregnant or lactating women

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. The MAH has previously performed successful user tests for other products. These tests confirm that any changes made to the proposed PL due to differences in formulation and the MAH's house style (related to formatting only) do not affect the readability of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Gefitinib Synthon 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 Synthon with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 11 July 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