26 July 2018
EMA/587444/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Gefitinib Mylan

International non-proprietary name: gefitinib

Procedure No. EMEA/H/C/004826/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

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List of abbreviations

AEs – adverse events

Al / Alu – Aluminium

ANOVA – Analysis of Variance

AP – Applicant's Part

API – Active Pharmaceutical Ingredient

AR – Assessment Report

ASD - amorphous solid dispersion

AS - Active substance

ASM – Active Substance Manufacturer

ASMF - Active Substance Master File=DMF – Drug Master File

BCS – Biopharmaceutics Classification System

BE – Bioequivalence

BMI – Body Mass Index

BSE/TSE – Bovine Spongiform Encephalopathy / Transmissible Spongiform Encephalopathy

CEP – Certificate of Suitability

CFU - Colony Forming Units

CHMP – Committee for Medicinal Products for Human Use

CoA – Certificate of Analysis

CPP - Critical process parameter

CQA – Critical quality attribute

CV – Coefficient of variation

DPM – Drug Product Manufacturer

DSC - Differential Scanning Calorimetry

EC - European Commission

EDQM – The European Directorate for the Quality of Medicines & HealthCare

EEA – European Economic Area

EGFR-TK - epidermal growth factor receptor tyrosine kinase

EMA – European Medicine Agency

EP - European Pharmacopoeia

EPAR – European Public Assessment Report

ERA - Environmental Risk Assessment

EU - European Union

FDA – Food and Drug Administration

FT-IR - Fourrier Transform Infrared Spectroscopy

GC – Gas Chromatography

GCP – Good Clinical Practice

GLP – Good Laboratory Practice

GMP – Good Manufacturing Practice

GVP – Good Pharmacovigilance Practices

HRMS - High resolution mass spectrometry

HPLC – High Pressure Liquid Chromatography

ICH – International Conference on Harmonisation

INN – International Non-proprietary Name

ICP-MS - Inductively coupled plasma mass spectrometry

IPC – In-Process Control

IR – Infrared spectroscopy

ISR – incurred sample reproducibility

KF - Karl Fischer titration

LC-MS – liquid chromatography-mass spectrometry

LOD – Loss of drying (1), Limit of Detection (2)

LOQ – Limit of Quantification

LoQ – List of questions

LS – least squares

MAA – Marketing Authorisation Application

MAH- Marketing Authorisation Holder

MO – Major objection

MS – Mass spectroscopy (1), Member State (2)

N/A – not applicable

NIR - Near Infrared Spectroscopy

NLT – not less than

NMR – Nuclear magnetic resonance spectroscopy

NMT – not more than

NSCLC - non-small cell lung cancer

OC – other concern

OOS - Out of Specification

PE – polyethylene

Ph. Eur. – European Pharmacopoeia

PI – Product of Information

PIL – Patient Information Leaflet

PK – pharmacokinetic(s)

PKWP – Pharmacokinetics Working Party

ppm - parts per million

PVC – polyvinyl chloride

PVDC – polyvinylidene chloride

QbD – Quality by Design

QC – Quality Control

QOS – Quality Overall Summary

QP – Qualified Person

q.s. – quantity sufficient

QTPP – Quality Target Product Profile

QWP - Quality Working Party

RH – Relative Humidity

RP – Restricted Part

RSD – Relative Standard Deviation

RUT – Readability User Test

SM - Starting Material

SmPC – Summary of Product Characteristics

TEAEs – treatment emergent adverse events

TTC - Threshold of toxicological concern

USP - United States Pharmacopoeia

USP/NF - United States Pharmacopoeia/National Formulary

UV - Ultraviolet

XR(P)D - X-Ray (Powder) Diffraction

1. Background information on the procedure

The applicant MYLAN S.A.S. submitted on 24 July 2017 an application for marketing authorisation to the European Medicines Agency (EMA) for Gefitinib Mylan, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004 – 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 April 2017.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication: Gefitinib Mylan 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.

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Iressa instead of non-clinical and clinical unless justified otherwise.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 8 years in the EEA:

- Product name, strength, pharmaceutical form: Iressa
- Marketing authorisation holder: AstraZeneca AB
- Date of authorisation: (24-06-2009)
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/09/526/001-002

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Iressa
- Marketing authorisation holder: AstraZeneca AB
- Date of authorisation: (24-06-2009)
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/09/526/001-002

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Iressa 250 mg film-coated tablet
- Marketing authorisation holder: AstraZeneca AB

- Date of authorisation: (24-06-2009)
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/09/526/001-002
- Bioavailability study number: HMG-P5-597

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.1. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Katarina Vučić

The application was received by the EMA on	24 July 2017
The procedure started on	17 August 2017
The Rapporteur's first Assessment Report was circulated to all CHMP members on	3 November 2017
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	16 November 2017
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	14 December 2017
The applicant submitted the responses to the CHMP consolidated List of Questions on	22 March 2018
The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	4 May 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	17 May 2018
The CHMP agreed on a List of Outstanding Issues in writing to be sent to the applicant on	31 May 2018
The applicant submitted the responses to the CHMP List of Outstanding Issues on	22 June 2018

The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	11 July 2018
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Gefitinib Mylan on	26 July 2018

2. Scientific discussion

2.1. Introduction

Lung cancer is an aggressive, heterogeneous, and life-threatening disease. It has been one of the most common cancers in the world for several decades (1.8 million new cases in 2012, 12.9% of all new cancers worldwide (GLOBOCAN 2012). In the EU, lung cancer is ranked as the fourth most frequent cancer; approximately 313,000 new cases were diagnosed in 2012 (Ferlay et al. 2013). Furthermore, lung cancer incidence rates were two-fold higher in males compared to females (1,241,601 and 583,100, respectively). It is also the most common cause of death from cancer worldwide, estimated to be responsible for nearly 1 in 5 cancer deaths (1.59 million deaths; 19.4% of all deaths from cancer) in 2012, including 168,000 deaths in the US and 268,000 deaths in Europe (GLOBOCAN 2012). NSCLC represents approximately 80 to 90% of all lung cancers (Cataldo et al 2011, Herbst et al 2008). For the minority of patients with NSCLC who have resectable disease, surgery offers the best chance of cure (Mountain 1997). Despite progress in early detection and treatment, NSCLC is most often diagnosed at an advanced stage and has a poor prognosis (Herbst et al 2008). Once NSCLC has progressed to a locally advanced or metastatic stage there is no cure and treatment is therefore focused on extending life, delaying disease progression, and improving symptoms and quality of life.

Progress in molecular biology has changed the therapeutic approach to NSCLC, and the treatment of advanced NSCLC can now be guided by the presence of certain mutations, e.g., epidermal growth factor receptor (EGFR), or anaplastic lymphoma kinase (ALK).

Since the discovery of the common somatic mutations in the kinase domain of EGFR in 2004 (Lynch et al 2004), NSCLC patients with activating EGFR mutations in exons 18-21 of EGFR (including L858R and exon 19 deletions [Ex19del], collectively described as EGFRm) are considered a subset of NSCLC in terms of pathogenesis, prognosis and treatment.

In recent years, studies have identified the presence of EGFR mutations in approximately 10% of patients with lung cancer in the European Economic Area (EEA) (Barlesi et al 2013, Esteban et al 2015, Gahr et al 2013, Rosell et al 2009). Overall, EGFR mutations have been found to be more frequent in never smokers, in patients with the adenocarcinoma histologic subtype, and in women. Their prevalence is also higher in East Asian patients than in Caucasian patients (ESMO clinical practice guidelines [Reck et al 2014]).

There is a large body of evidence showing consistent efficacy of EGFR TKIs in patients with sensitizing EGFR mutations and that these patients are more likely to benefit from initial treatment with an EGFR TKI in preference to doublet chemotherapy (Maemondo et al 2010, Mitsudomi et al 2010, Mok et al 2009, Rosell et al 2012, Zhou et al 2011, Wu et al 2014).

First- or second-generation EGFR TKIs (gefitinib, erlotinib, afatinib) would generally be considered first choice treatment for patients with activating mutations in EGFR, offering ORRs of approximately 60-70% and

median PFS of 9 to 14 months (NCCN guidelines, ESMO clinical practice guidelines [Reck et al 2014], Sebastian et al 2014).

A majority of patients develop resistance to EGFR-TKIs with the most common resistance being associated with secondary T790M mutation. A 3rd generation TKI (osimertinib) has been authorised for the treatment of patients harbouring the T790M mutation and most recently for the 1st line treatment of NSCLC with activating EGFR mutations.

This application for a marketing authorisation of Gefitinib Mylan 250 mg film-coated tablets concerns a generic application of a centrally authorised medicinal product according to Article 10(1) of Directive 2001/83/EC.

The reference product is Iressa 250 mg film-coated tablets registered by AstraZeneca AB, S-151 85, Södertälje, Sweden. The community granted marketing authorisation of the reference product Iressa 250 mg film-coated tablets on 24/06/2009 under number EMEA/H/C/001016.

In line with the originator Iressa 250 mg film-coated tablets, the targeted indication for Gefitinib Mylan 250 mg film-coated tablets is the following:

"Gefitinib Mylan 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 4.4)."

The recommended posology of Gefitinib Mylan is one 250 mg tablet once a day. The tablet may be taken orally with or without food, at about the same time each day. The tablet can be swallowed whole with some water or if dosing of whole tablets is not possible, tablets may be administered as a dispersion in non-carbonated water.

Gefitinib is a selective small molecule inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase and can be a treatment option for patients with tumours with activating mutations of the EGFR tyrosine kinase domain. No clinically relevant activity has been shown in patients with known EGFR mutation negative tumours.

2.2. Quality aspects

2.2.1. Introduction

The finished product presented as an immediate release film-coated tablets containing 250 mg of gefitinib as active substance.

Other ingredients in the tablet core are lactose monohydrate, microcrystalline cellulose (101), crospovidone (type A), povidone (K30), sodium laulyl sulfate and magnesium stearate. The film coating comprises polyvinyl alcohol (E1203), macrogol 4000 (E1521), talc (E553b), titanium dioxide (E171), red iron oxide (E172) and yellow iron oxide (E172), as described in the SmPC section 6.1.

The product is available in PVC/PVDC/Aluminium blisters or PVC/PVDC/Aluminium perforated unit dose blisters, as described in section 6.5 of the SmPC. The blisters may be packed into aluminium pouches

2.2.2. Active substance

General information

The chemical name of gefitinib is *N*-(3-Chloro-4-fluorophenyl)-7-methoxy-6-[3-(morpholin-4-yl)propoxy]quinazolin-4-amine corresponding to the molecular formula $C_{22}H_{24}ClFN_4O_3$. It has a molecular mass of 446.90 g/mol and the following structure (**Figure 1**):

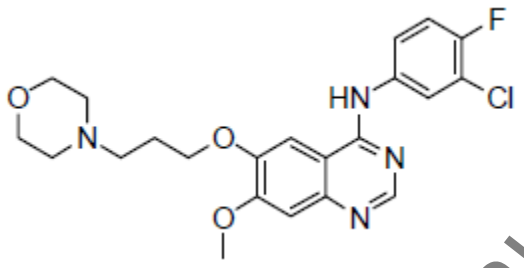

Figure 1. Structure of gefitinib.

The structure has been elucidated using high resolution mass spectrometry (HRMS), UV spectroscopy, infrared spectroscopy (FT-IR), nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) spectroscopy, mass spectrometry (MS), differential scanning calorimetry analysis (DSC) and X-ray diffraction analysis (XRD).

Gefitinib is described in the Ph. Eur. monograph 2866. It appears as a white or almost white, non-hygroscopic, crystalline powder. It is practically insoluble in water. Sufficient information on the solubility in aqueous buffers has been provided: solubility increases with decreasing pH. The molecule has two pKa of 5.4 and 7.2 and its partition coefficient logP is 3.75 (octanol/water).

Gefitinib exhibits polymorphism as reported in the literature. The active substance (AS) produced by the proposed manufacturer is Form 1. Gefitinib polymorphic form is characterised by X-ray powder diffraction and is controlled in the specification.

One structural isomer (Ph. Eur. Impurity B) is the potential impurity in the manufacturing process of Gefitinib and is controlled as specified impurity with limit of NMT 0.2% in the specification of final active substance, which is consistent with Ph. Eur. monograph.

Manufacture, characterisation and process controls

The ASMF procedure is used for the drug substance. Detailed information on the manufacturing process of the active substance has been provided in the restricted part of the ASMFs and it was considered satisfactory. Gefitinib is sourced from one manufacturer. Two ASMFs have been submitted as different synthesis routes are applied for production of the same crystalline form (Form 1). Gefitinib from both routes is manufactured in 5 steps from the same starting materials (SMs).

The two processes differ mainly in the crystallisation and purification processes in steps (e.g. solvent system, temperatures, drying times) applied to the intermediates and the final active substance but not in the chemical synthesis steps. It has been demonstrated that the same polymorphic form of gefitinib is consistently produced by the two processes and that the polymorphic form remains unchanged following storage at long term and accelerated conditions.

Tests for identification, purity and related substances (specified, unspecified and total impurities) are included in the specification of the SMs. The carry-over of impurities from SMs has been addressed including justification for the proposed limits for specified impurities and other single impurities in the specification of SMs. Palladium (Pd) is used in the manufacturing process of SM1 and carry-over of Pd from SM1 into the AS has been studied with a validated ICP-MS method. The test for palladium is performed as skip testing. This is acceptable since palladium was found below 30% of ICH Q3D option 1 limit in 3 consecutive batches of

gefitinib. It is stated that no other catalyst is used during the manufacturing process of gefitinib.

Four intermediates (Gefitinib amides, Gefitinib hydrolysates, Gefitinib crude and 1st purified Gefitinib) are isolated, for which the specifications and analytical procedures were provided and are considered acceptable. Several critical steps in the manufacture of Gefitinib have been identified. The acceptance criteria and test procedures for the in-process controls have been described and are considered satisfactory.

The characterisation of the active substance and its impurities is in accordance with the EU guideline on chemistry of active substances. Potential and actual impurities were well discussed with regards to their origin and characterised. The potential genotoxicity of all chemical substances including raw materials, reagents, catalyst and corresponding impurities have been analysed in accordance with ICH M7 guideline. The structures of all chemical substances involved in the production process of gefitinib have been presented. 3-Chloro-4-fluoroaniline has been identified as potential genotoxic impurity, which is controlled in gefitinib drug substance. No residual solvent has been observed above Q3C recommended limits in the active substance batches.

The active substance is stored in double polyethylene (PE) bags placed in aluminium tin with rubber rim and aluminium cap. This primary packaging complies with EC directive 10/2011 as amended and the specification includes test for identification by IR.

Specification

Gefitinib specification includes tests for: appearance, identification (IR, HPLC), related substances (HPLC), 3-chloro-4-fluoroaniline content (LC-MS), water content (Ph. Eur.), sulfated ash (Ph. Eur.), residual solvents (GC), assay (HPLC), polymorphism (X-RD), particle size (laser diffraction) and microbiological quality (Ph. Eur.). The specification and acceptance criteria for gefitinib are established based on the current version of the Ph. Eur. monograph.

The specification for gefitinib applied by the finished product manufacturer has been amended in line with the latest versions of specifications in each ASMF. XRD has also been included as a non-routine test in the updated active substance manufacturer's specification of gefitinib.
The limits proposed for residual solvents are those given in ICH Q3C guideline and are therefore acceptable. The proposed limits for assay, water content and sulfated ash are in line with the Ph. Eur. monograph for gefitinib.

The requirements for microbiological purity are in line with the criteria presented in Ph. Eur. General Text 5.1.4 with additional requirement for absence of the specified microorganism E. coli.

3-Chloro-4-fluoroaniline has been identified as potential genotoxic impurity and is controlled in gefitinib active substance based on the threshold of toxicological concern (TTC) (≤1.5µg/day). Considering the maximum daily dose of gefitinib (250 mg) the acceptance criteria has been established using in-house LC-MS method. The impurity was found absent in three batches of gefitinib drug substance.

Benzene is tested within the specifications of the solvents used during the synthesis. The absence of benzene in the active substance has also been demonstrated by batch analysis data.

The analytical methods used have been adequately described and and are in line with those in the Ph.Eur. monograph for gefitinib. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data from 3 commercial scale batches from each commercial process were provided. The results are within the specifications and consistent from batch to batch and demonstrated the equivalence of the two processes.

Stability

Stability data on three commercial scale batches of gefitinib from each of the two processes placed under long term conditions (30±2 ºC / 65±5% RH) for up to 36 months and accelerated conditions (40±2 ºC / 75±5% RH) for six months were provided according to the ICH guidelines. In addition, data from two commercial batches (process I) were provided under long term conditions with higher relative humidity (30±2 ºC / 75±5% RH) for up to 24 months as well as under standard accelerated conditions (40±2 ºC / 75±5% RH) for up to 6 months. The stability samples were stored in sealed double layers of PE bags (immediate packaging material) and then put in a sealed aluminium tin (secondary packaging material) that are fully representative of the commercial active substance packaging (simulated commercial packaging).

The following parameters were tested during stability studies: appearance, loss on drying initially, then replaced by water content, assay, related substances, 3-chloro-4-fluoroaniline content and microbial limits test. The stability indicating nature of the HPLC methods for assay and related substances was demonstrated by forced degradation studies. All results for tested parameters remained within specifications during the investigated period under long term conditions. No obvious trends or significant changes were observed, except for a negligible increase in the level of total impurities from the initial value at both long term and accelerated conditions for two batches.

One commercial scale batch of gefitinib from each process was subjected to stressed degradation study to evaluate potential degradation products and to demonstrate stability indicating nature of the HPLC methods for assay and related substances. Gefitinib samples were exposed to stress conditions including acid degradation, alkaline degradation, oxidative, water hydrolysis, exposure to elevated temperature, high humidity and light exposure (ICH Q1B conditions). According to the presented results gefitinib is not sensitive to heat, moisture and it is not photosensitive. It is sensitive to oxidation and to lesser extent, to hydrolysis under different conditions. The proposed container closure system provides adequate protection to the active substance.

Based on the provided stability results, the proposed retest period of 24 months for the active substance, without special storage conditions is justified in both ASMFs.

2.2.3. Finished medicinal product

Description of the product and pharmaceutical development

The finished product is brown, round, biconvex immediate release film-coated tablets available in 250 mg strength.

The aim of the pharmaceutical development was to develop a generic product to the reference product Iressa. Gefitinib is highly lipophilic (LogP ~4) and is classified as class 2 compound (low solubility – high permeability) according to the biopharmaceutical classification system (BCS). Evaluation of the main characteristics (physical-chemical characterisation) of Iressa 250 mg film-coated tablets was performed on three batches obtained from the major European markets of this product. Also, dissolution profiles in pH 1.2, pH 4.5 and pH 6.8 dissolution media without surfactant (paddles, 50 rpm, 1000 ml) showed there is no significant difference in dissolution behaviour at pH of 1.2 and no significant difference in dissolution behaviour comparing reference product batches from different countries at pH 4.5. However, at pH 6.8,

dissolution is below 5%. Based on active substance characteristics and reference product characterisation data, a quality target product profile (QTTP) was defined for the generic Gefitinib 250 mg film-coated tablets .

The excipients used in Gefitinib Mylan were selected based on the excipients used in the reference product, excipient compatibility studies and development results (dissolution and stability data) and are commonly used for tabletting purposes.

Excipient/active substance compatibility was assessed through HPLC analysis of binary mixtures of varying ratios. Water was added to mimic the wet granulation process. Each mixture was stored and then analysed for degradation products and organoleptic characteristics. All excipients studied are considered compatible because no significant increase in impurity level was observed after 3 and 7 days of storage. The selection of suitable grade of excipients was based on the results of the compatibility studies, reference product formulation and previous formulation knowledge for similar wet granulation products.

The tablet weight was set at 500 mg in line with the reference product. The drug load in the generic formulation was fixed at 50% based on the reference product label, strength and tablet weight.

The influence of the levels of diluents, wetting agent, disintegrant, binder, lubricant and film-coating agent on dissolution profile was studied and based on the results, a final formulation was selected.

A solubility study has been carried out and showed that gefitinib is soluble in pH 1.2 and pH 4.5 aqueous media and that sink conditions are achieved. Gefitinib is practically insoluble in dissolution media of pH 5.4, pH 6.8 and pH 7.2. The FDA recommended dissolution medium for this product is Tween 80 (5% v/v) in water. The solubility in the FDA dissolution medium is lower than pH 1.2 and pH 4.5, although sink conditions are reached too. Dissolution profiles of the test and reference products were measured in the different dissolution media (pH 1.2, pH 4.5, pH 6.8 and FDA dissolution medium). The results indicate that the dissolution is very fast at pH 1.2 and that at pH 6.8, gefitinib is not dissolved sufficiently. Both the pH 4.5 and FDA dissolution media could be chosen as routine QC medium. Sink conditions were achieved in both these media. The discriminatory power of the method was evaluated with different variants of the final tablet formulation (excipient ratios) and process parameters (wet granulation step). The chosen dissolution method was found to be sufficiently discriminatory.

A bioequivalence study was performed. As per the bioequivalence guideline comparative dissolution study of the reference product and BE test batch was conducted at pH 1.2, 4.5, and 6.8. At pH 1.2, more than 85% of AS is dissolved in 15 min, and thus, no further evaluation is required, profiles are deemed similar. For the other two media (pH 4.5 and pH 6.8) the dissolution profiles are also similar by visual observation and by method of calculation of the Mahalanobis distance and the results of statistical comparison revealed that the profiles are similar. Dissolution profiles of 2 other validation batches were compared to the dissolution profile of the test product (bio-batch) and were found to be similar too. Additionally, assay and impurities profiles of the reference and the test products were compared and found to be comparable.

According to the SmPC, tablets may be administered as dispersion in water (non-carbonated) and, additionally, the dispersion can also be administered through a naso-gastric or gastrostomy tube. Since qualitative and quantitative composition of the test and the reference products are not the same, and considering that bioequivalence was demonstrated only on whole tablets, but not with dispersion, additional *in vitro* studies were performed comparing test and reference products. The provided results demonstrated the similarity between the test and the reference products, when tablets are administered as dispersions in water and through a nasogastric or gastrostomy tube as per SmPC section 4.2.

Manufacturing process development

Some formulations were prepared in order to study the influence of manufacturing processes on the polymorphic stability of the active substance. Samples prepared by direct compression (final mixture), aqueous granulation and organic granulation processes were studied. They were found to be essentially the same. It can be shown that these three formulations contain the same crystalline form of the AS as that of reference product. All of them were introduced in stability chambers to study the AS stability. The formulation prepared by direct compression (final mixture) gave worse stability results than the other two prepared by wet granulation. Both granulated trials presented similar (slightly better) stability results than the reference product.

The use of wet granulation with an aqueous solvent instead of an organic solvent was preferred because of the desire to avoid the environmental considerations involved. Dissolution profiles of tablet samples manufactured by aqueous solvent instead of an organic solvent were measured in QC dissolution medium in order to study the influence of the granulation solvent. Organic solvents were found to slow down the dissolution rate. Based on the results an aqueous granulation process was selected as the process for further drug product development efforts.

A risk assessment of the overall drug product manufacturing process was performed to identify the high risk steps that may affect the CQAs of the final drug product. Assay, dissolution and degradation products were the identified product CQAs.

A further risk assessment was performed subsequently on each identified high risk process step to evaluate which process variables may potentially impact the CQAs of the drug product.

In the initial risk assessment of the manufacturing process wet granulation, sieving and compression were highlighted as high risk considering their impact on dissolution. Respective Design of Experiments (DoE) trials were performed for these steps. Based on the DoE results, the manufacturing process parameters that could potentially impact the CQAs of the finished product were identified and their associated risk was evaluated and the control strategy was defined.

Evaluation of elemental impurities according to ICH Q3D has been provided. The contribution of each component and process to the final content of elemental impurities in the drug product has been discussed. The synthesis of gefitinib active substance is stated by the manufacturer not to employ metal catalysts. The starting material derives from chemical synthesis involving palladium (Class 2B). Factual batch data was provided and a safe maximum concentration of <5 µg/g of Pd is estimated for this precursor. For this reason it has been considered that no relevant presence of this and any other metal impurity in the AS should be expected.

All excipients, except for povidone, have been certified according to EMA guideline EMA/CHMP/SWP/4446/2000. Povidone, the synthesis of which is known to take place in the presence of copper, comes certified as compliant to EMA guideline. All specific reported values provided for the rest of elemental impurities are far from reference calculated values.

Water used in the manufacturing processes meets the current Ph. Eur. requirements for purified water for conductivity and heavy metals, and as such, the risk of inclusion of elemental impurities from water is negligible.

Gefitinib 250 mg film-coated tablets are packed in PVC/PVDC/Aluminium blister packs. The blister strips are packed in printed cartons. Additionally the blisters may be packed into aluminium pouches. All immediate packaging materials comply with the requirements of Commission Regulation (EU) No 10/2011, as amended.

Manufacture of the product

The manufacturing process comprises the following main steps: blending, wet granulation, drying, sieving, blending, tableting, film coating and packaging.

The manufacturing process of Gefitinib Mylan film-coated tablets is a standard process, widely used in the pharmaceutical industry. Critical steps were identified as wet granulation, drying, tabletting (compression) and coating and adequate IPCs have been established. Process validation has been carried out on three consecutive commercial scale batches. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Product specification

The release and shelf-life specifications for the finished products include appropriate tests and limits for: appearance (visual), identity of active substance (HPLC, UV), assay (HPLC), related substances (HPLC), 3-chloro-4-fluoroaniline content (LC-MS), dissolution (Ph. Eur. - HPLC), uniformity of dosage units (mass variation - Ph. Eur.) and microbiological quality (Ph. Eur.).

Limits for impurities are set according to ICH Q3B considering the daily dose of gefitinib is 250 mg. The limit for dissolution is in line with dissolution results of bio-batch and *Reflection paper on the dissolution specification for generic oral immediate release products*. Testing of the potentially genotoxic impurity, which is also a degradation product, 3-chloro-4-fluoroaniline is included in the finished product specification with a limit according the threshold of toxicological concern (TTC) concept. Testing of 3-chloro-4-fluoroaniline is also included in the stability study. The proposed limit for 3-chloro-4-fluoroaniline is acceptable and in line with ICH M7.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch results from four commercial scale batches have been presented, demonstrating compliance with the proposed specifications and consistency in manufacture.

The finished product is released on the market based on the above release specifications, through traditional finished product release testing.

Stability of the product

Stability data was provided for four commercial scale batches under long term conditions (25 °C ± 2 °C / 60% ± 5% RH and 30 °C ± 2 °C / 75% ± 5% RH) for up to 24 months and under accelerated conditions (40 °C ± 2 °C / 75% ± 5% RH) for 6 months according to the ICH guidelines. Stability batches were manufactured using AS synthesized by each of the two processes. All samples were packed in PVC/PVDC/Alu blister intended for marketing and some samples were additionally packed in Aluminium pouches.

Tests performed were appearance, assay, related substances, microbiological quality and dissolution. The methods for assay and related substance are stability indicating. Under all storage conditions, results for all tested parameters of batches packed with and without pouches except one of the tested paraeters were well within the applied acceptance criteria. Under accelerated storage conditions, out of specification results for one of the tested paraeters were obtained for both pouched and unpouched samples, at the 6 month testing point. Due to the significant change for one of the tested paraeters after 6 months under accelerated conditions stability data under long-term conditions (30 °C/75% RH) were presented (as already mentioned

above). The results of all batches were well within the applied acceptance criteria after 24 months at 25 °C / 60% RH and after 12 months at 30 °C / 75% RH.

Stability studies on tablets packed in bulk packaging material (double PE bag) were performed on one commercial scale batch for up to 3 months at 40 °C / 75% RH and 12 months at 25 °C / 60% RH. During storage the product did not show any significant changes in the parameters tested, i.e. appearance, assay, related substances, dissolution and microbiological quality. Hence, the proposed holding time for Gefitinib 250 mg film-coated tablets in bulk packaging is 12 months.

Based on the stability data presented, the proposed shelf life of 24 months and storage conditions ("Do not store above 30 °C.") in both packaging configurations are acceptable.

Adventitious agents

All excipients with the exception of lactose monohydrate used for the production of Gefitinib Mylan 250 mg film-coated tablets are of synthetic, vegetable or mineral origin.

It is confirmed that the lactose used in the manufacture of Gefitinib Mylan is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

None.

2.3. Non-clinical aspects

2.3.1. Introduction

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. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Gefitinib Mylan manufactured by Mylan S.A.S. is considered unlikely to result in any significant increase in the combined sales volumes for all gefitinib containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

2.3.3. Discussion on non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of gefitinib are well known. Published literature has been reviewed and is considered of suitable quality.

In line with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00), the justification for not providing new ERA studies is acceptable.

2.3.4. Conclusion on the non-clinical aspects

A summary of the literature with regard to non-clinical data of Gefitinib Mylan and justifications that the active substance does not differ significantly in properties with regards to safety and efficacy of the reference product was provided and was accepted by the CHMP. This is in accordance with the relevant guideline and additional non clinical studies were not considered necessary.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for film-coated tablets containing gefitinib. To support the marketing authorisation application the applicant conducted one bioequivalence study with cross-over design under fasting conditions. This study was the pivotal study for the assessment.

The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of gefitinib based on published literature. The SmPC is in line with the SmPC of the reference product.

For the clinical assessment the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98) as well as the Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/09), Question number 3.6 of the Questions & Answers: Positions on specific questions addressed to the Pharmacokinetics Working Party (EMEA/618604) in their current version, are of particular relevance.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Exemption

Question number 3.6 of the Questions & Answers: Positions on specific questions addressed to the Pharmacokinetics Working Party (EMEA/618604) allows the waiver for drug substances of BCS classification class 1 or 3. Based on the EMA Q&As, the same cannot be concluded for BCS class 2 drugs like gefitinib.

As the drug substance needs to be solubilized in order to be absorbed, comparing intact tablets in vivo could generally be considered most sensitive as this would include disintegration and dissolution processes. However, published data demonstrate, that bioavailability could change substantially after crushing/dispersing tablets. As an example, reduced bioavailability as compared to the intact tablet has been described for artemether though not for lumefantrine with a fixed dose combination (Abdulla et al. Malaria Journal 2010, 9:253). Further, the product-specific bioequivalence guideline for everolimus (published on the EMA website) requires separate bioequivalence testing for the dispersed tablets in addition to the study with intact tablets.

Accordingly, formulation related differences and changes in bioavailability after dispersion cannot be completely excluded all the more gefitinib is considered BCS class 2 and formulation effects could be expected to be more relevant as compared to highly soluble compounds (BCS 1 and 3).

However, the relative bioavailability of the originator IRESSA (gefitinib 250 mg) administered as a tablet or as a tablet dispersion (drink and tube administered) was investigated in a pharmacokinetic study in 18 healthy male volunteers. The pharmacokinetic parameters (AUC, Cmax, tmax and t½) investigated in this study were found to be similar following each method of administration of a single 250 mg tablet of the originator IRESSA (EPAR; study 0229).

The additional administration process “as a dispersion in water” in line with the SmPC was not adequately justified in the initial application. Therefore, a thorough justification for a biowaiver for an additional study of the dispersed tablets was requested as part of the Day 120 list of questions in order to exclude the possibility of bioinequivalence compared to the originator IRESSA when Gefitinib Mylan is administered as dispersion in water (drink or tube administered). Given that the innovator demonstrated similarity for both modes of administration this justification should be based on a thorough comparison of the composition of test and reference product. Furthermore, the applicant was requested to perform meaningful comparative in vitro investigations in order to substantiate the negligible impact of formulation related differences. The originator’s SmPC indicates that dispersion may need 20 minutes even with frequent swirling and the suspension should be administered within 60 min. These time frames should be considered not only in terms of comparable disintegration times of the generic but also in terms of stability of the drug substance.

During the procedure, the applicant provided a thorough comparison of Quality attributes (see Quality section of this AR).

Clinical studies

To support the application, the applicant has submitted one bioequivalence study.

Table 1 Tabular overview of clinical studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BE	HMG-P5-597	clin-stud-rep-hmg-p5-597.pdf	To evaluate and compare the bioavailability and therefore to assess the bioequivalence of two different formulations of gefitinib after a single oral dose administration under fasting conditions.	Single center, randomized, single dose, laboratory-blinded, 2-period, 2-sequence, crossover design.	250 mg single dose; oral Fasting conditions	48	Healthy Subjects	Single dose	Complete; Full

2.4.2. Pharmacokinetics

Study HMG-P5-597: Single dose crossover comparative bioavailability study of gefitinib 250 mg film-coated tablets in healthy male and female volunteers*Methods*

Study design

Study no HMG-P5-597 was an open-label, laboratory-blinded, randomized, single dose, two-period, two-treatment cross-over bioequivalence study in healthy adult male and postmenopausal female subjects under fasting conditions with a wash out period of 21 days between two administrations.

The application concerns an oral immediate release formulation. According to the SmPC of the Iressa no specific recommendation regarding food intake is given for Gefitinib posology. Therefore, the conduct of the single dose study under fasting condition as most sensitive condition to detect a potential difference between formulations is considered adequate.

Administrative data

Protocol No.: HMG-P5-597 (final protocol dated 2016/04/26)

Study Periods:

Clinical:

First dose to date of last subject visit: 2016/05/21 to 2016/06/14

Period I: FPFV: 2016/05/20 LPLV: 2016/05/24

Period II: FPFV: 2016/06/10 LPLV: 2016/06/14

Bioanalytical:

Experimental phase: 2016/06/16 - 2016/06/27

Samples received: 2016/05/25 (1. shipment), 2016/05/26 (2. shipment) and 2016/06/15 (3. shipment)

Food and fluid intake

Food was controlled and standardized for each housing period and for all subjects. Subjects fasted overnight for at least 10 hours prior to drug administration and until approximately 4 hours after drug administration,

when a standardized lunch was served. A supper and a light snack (and other meals) were served at appropriate times thereafter, but not before 9 hours after drug administration.

Fluid intake other than water was controlled for each housing period and for all subjects. Water was provided ad libitum until 1 hour predose; the drug was given with about 240 mL (8 oz.) of water at room temperature; water was allowed ad libitum beginning 1 hour after the administration of the drug.

Posture and physical activities

Subjects were asked to remain seated or ambulatory for the first 4 hours following drug administration, avoiding both vigorous exertion and complete rest. However, should adverse events have occurred at any time, subjects may have been placed in an appropriate position. Subjects were asked not to engage in strenuous activity at any time during the housing periods. During each period of the study, bathrooms were locked for at least 4 hours after each drug administration. When necessary, subjects were permitted to use the washroom facilities under supervision only during this interval.

Sampling schedule

Twenty blood samples were collected for the assessment of Gefitinib in plasma. Blood collections were performed prior to the administration of study medication (0 pre-dose) and at 0.50, 1.00, 2.00, 3.00, 4.00, 4.50, 5.00, 5.50, 6.00, 6.50, 7.00, 8.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00, and 72.00 hours after study drug administration. Treatments were separated by a washout period of 21 days. The sampling time schedule and washout period is considered adequate taking into account the elimination half-life of the drug (about 41 hours).

Test and reference products

Test product:

Gefitinib 250 mg film-coated tablet
manufacturing date: December 2015
expiry date: June 2016 (on-going stability program)
Reference product:

Iressa 250 mg film-coated tablet (MA no. EMEA/H/C/001016)
expiry date: December 2018

Populations studied

Beside others, subjects with history of significant hypersensitivity to gefitinib or any related products (including excipients of the formulations) as well as severe hypersensitivity reactions (like angioedema) to any drugs, presence of significant gastrointestinal, liver or kidney disease, or any other conditions known to interfere with the absorption, distribution, metabolism or excretion of drugs or known to potentiate or predispose to undesired effects, history of significant gastrointestinal, liver or kidney disease that may have affected drug bioavailability and presence of significant cardiovascular, pulmonary, hematologic, neurological, psychiatric, endocrine, immunologic or dermatologic disease, have been excluded.

The study population included healthy postmenopausal female and male volunteers aged 18-55 years, with a body mass index (BMI) ≥ 18.5 and ≤ 30 kg/m^2.

Analytical methods

Plasma concentrations of Gefitinib were determined using a validated reversed phase HPLC-MS/MS method. Precision and accuracy of Gefitinib in human plasma were determined at LOQ, low, medium, and high QC sample concentrations. For each precision and accuracy batch, each QC concentration level were assayed within a single batch. Between-run and within-run precision and accuracy results were provided in the Validation report and were found acceptable.

The first blood plasma samples were taken 2016-05-21 and the bioanalytical part was completed at 2016-06-28. Stability for the analyte in plasma (long term stability) was shown for 72 days at -80°C nominal. Therefore, the actual longest storage period of the study samples of 37 days is well covered.The reproducibility of the bioanalytical method was evaluated by the repeated analysis of some study samples (incurred sample reproducibility (ISR)). At least 10% of the first 1000 analysable study samples and 5% of the remaining analysable study samples were re-assayed and compared to the original values. For Gefitinib, 150 samples have been re-assayed as ISR, and on the 150 evaluable samples re-assayed, 145 samples (96.7 %) have met the percent difference criterion of ≤20.0%.
At least 2/3 of the total samples selected for ISR evaluation have met the percent difference criteria of ≤20.0% between original and re-assayed concentrations.

Pharmacokinetic variables

The main pharmacokinetic parameters of interest for this study were:

• **AUC_{0-72h}**: area under the curve of plasma concentration versus time [ng·h/mL] calculated by the linear trapezoidal rule from sampling time zero to the sampling time of 72 h.

• **$AUC_{0-\infty}$**: area under the curve of plasma concentration versus time [ng·h/mL] from time zero to infinity.

• **C_{max}**: maximum plasma concentration measured [ng/mL].

• **t_{max}**: the time [h] of the maximum measured plasma concentration.

• **Terminal rate constant (λ_z)**: terminal elimination rate constant [h^{-1}].

• **Terminal Half-life ($t_{1/2}$)**: the elimination or terminal half-life [h].

Primary PK-parameters were C_{max} and AUC_{0-72h} and acceptable.

Statistical methods

The natural logarithmic transformation of C_{max}, and AUC_{0-72} and $AUC_{0-\infty}$ was to be used for all statistical inference.

The parameter t_{max} was to be analyzed using a non-parametric approach. Test of fixed period, sequence and treatment effects were to be based on the Wilcoxon's rank sum test (Mann-Whitney U-test). When appropriate (e.g. small or sparse sample), the exact version of the test was also to be presented.

All other pharmacokinetic parameters were to be statistically analyzed using an Analysis of Variance (ANOVA) model. The fixed factors included in this model were to be the subject effect (nested within sequence), the treatment received, the period at which it was given, as well as the sequence in which each treatment is received.

For conclusion of bioequivalence, the ratio of geometric LS means with corresponding 90% confidence interval calculated from the exponential of the difference between the Test and Reference for the ln-transformed parameters C_{max} and AUC_{0-72} were all to be within the 80.00 to 125.00% bioequivalence range.

Results

Table 2 Pharmacokinetic parameters for Gefitinib (non-transformed values)

Pharmacokinetic parameter	**Test N=44**		**Reference N=44**	
	arithmetic mean geometric mean	SD CV%	arithmetic mean geometric mean	SD CV%
$AUC_{(0-72)}$ (ng*h/ml)	**3785.54** 3414.00	± 1653.23 43.7 %	**3903.68** 3544.50	± 1637.05 41.9%
$AUC_{(0-\infty)}$ (ng*h/ml)	**4112.91** 3658.74	± 1889.82 45.9 %	**4180.00** 3760.49	± 1780.94 42.6 %
C_{max} (ng/ml)	**158.02** 142.67	± 73.26 46.4 %	**154.38** 143.84	± 59.51 38.5 %
T_{max}* (h)	6.25	3.0 – 10.00	6.25	4.00 – 12.00

AUC_{0-72} area under the plasma concentration-time curve from time zero to 72 hours

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity

C_{max} maximum plasma concentration

T_{max} time for maximum concentration (* median, range)

Table 3 Statistical analysis for Gefitinib (ln-transformed values)

Pharmacokinetic parameter	**Geometric Mean Ratio Test/Reference**	**Confidence Intervals**	**CV***
$AUC_{(0-72h)}$ (ng*h/ml)	96.32 %	91.56 – 101.32 %	14.20 %
$AUC_{(0-\infty)}$ (ng·h/mL)	97.29 %	92.03 – 102.86 %	14.43 %
C_{max} (ng/ml)	99.19 %	91.39 – 107.66 %	23.15 %

* estimated from the Residual Mean Squares

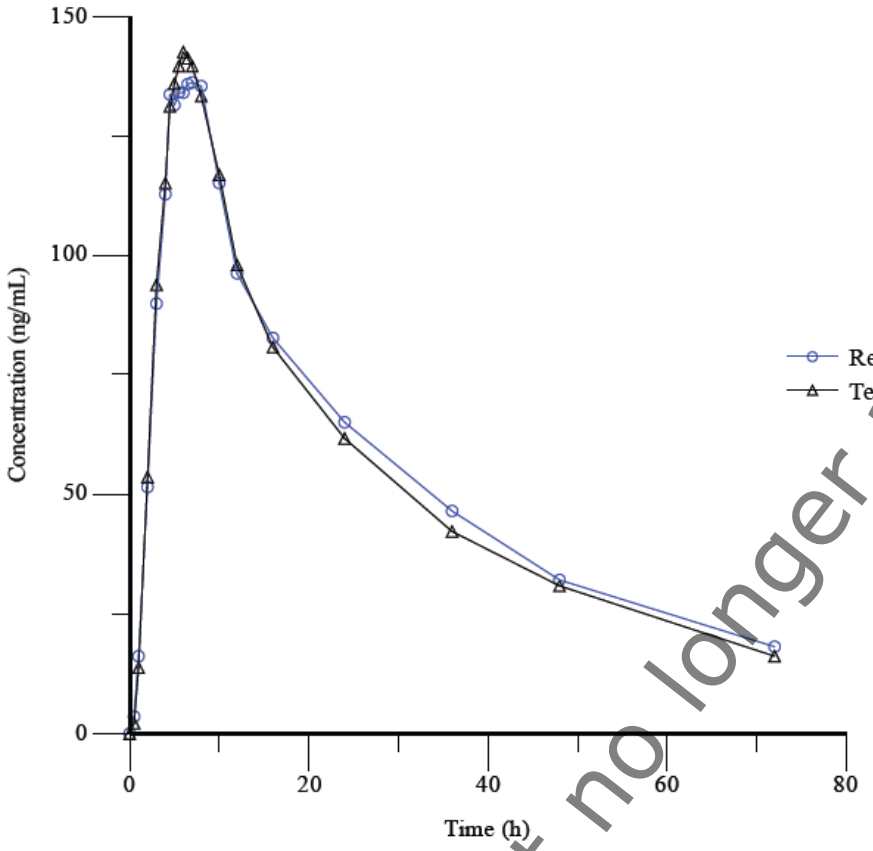

Figure 2 Linear plot of mean plasma concentrations of Gefitinib after administration of Test and Reference formulations (250 mg) to healthy subjects (N=44).

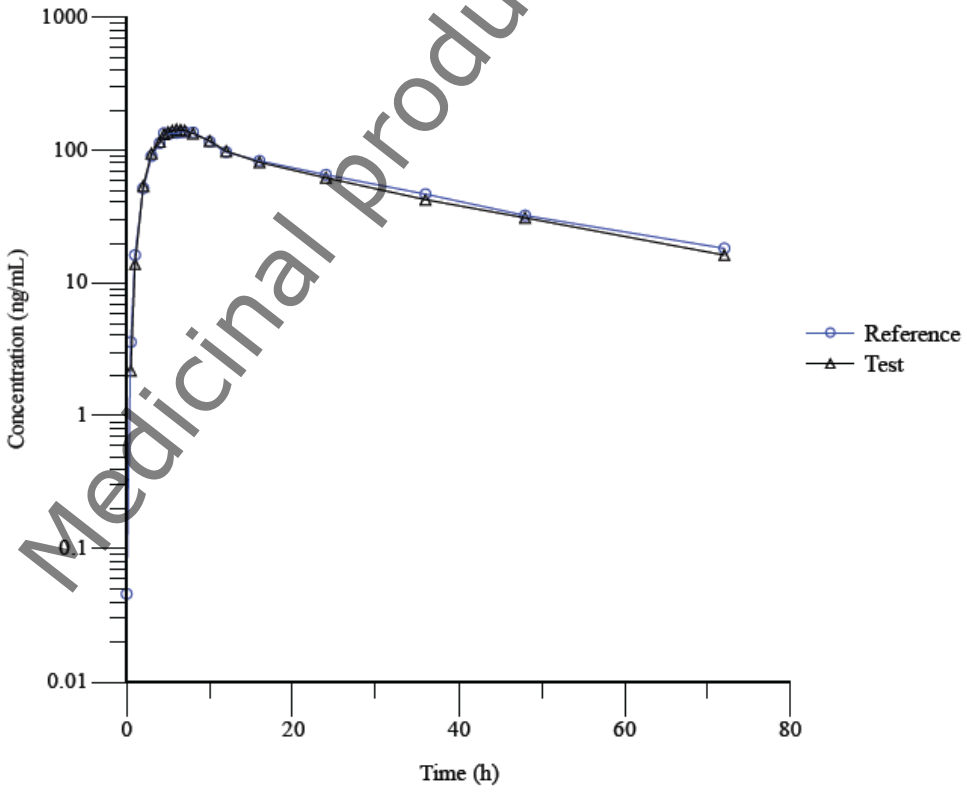

Figure 3 Semi-logarithmic plots of mean plasma concentrations of Gefitinib after administration of Test and Reference formulations (250 mg) to healthy subjects (N=44).

As indicated in the tables and figures above, the 90% confidence intervals for ln-transformed pharmacokinetic variables C_{max} and AUC_{0-72h} were within the conventional bioequivalence range of 80% to 125%.

Safety data

No serious adverse events (AEs) occurred. One subject (029) was withdrawn from the study by the investigator for safety reasons before dosing of period 2 due to a mild abscess (at right armpit), judged not related to the administration of Gefitinib, and the concomitant medication administered.

A total of 45 TEAEs were reported by 20 (42%) of the 48 subjects who participated in this study; 29 (64%) TEAEs were considered related to drug administration. Of the 45 TEAEs reported during the study, 13 occurred after administration of the Test and 32 after administration of the Reference.

The TEAEs reported most commonly in this study were headache, experienced by 3 subjects (7%) after administration of only the Reference, and dizziness, experienced by 1 subject (2%) after administration of the Test and 2 subjects (4%) after administration of the Reference. Acne was experienced by 2 subjects (4%) after administration of only the Test and back pain was experienced by 2 subjects (4%) after administration of only the Reference. The remaining TEAEs were experienced by no more than 1 subject (2%) per treatment group.

The incidence of TEAEs was slightly higher in the subjects administered the Reference (33%) than in the subjects administered the Test (22%). The incidence of drug-related TEAEs was also slightly higher in the subjects administered the Reference (13% for Test, 24% for Reference).All the abnormal clinical laboratory values were marginally higher or lower than their reference ranges and none were considered clinically significant by the investigator.

In the limited safety population no new safety signals became obvious.

Conclusions

Based on the presented bioequivalence study Gefitinib Mylan is considered bioequivalent with Iressa.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.5. Discussion on clinical aspects

Based on the presented bioequivalence study Gefitinib Mylan 250 mg film-coated tablets is considered bioequivalent with Iressa 250 mg film-coated tablets by AstraZeneca UK Ltd. Based on the provided thorough

justification in the Applicants Response, the results of study HMG-P5-597 can also be extrapolated to the dispersed tablets (see Quality Assessment for details).

During the procedure, the applicant provided further information on the outcome of the inspections performed by competent authorities/EU inspectors. Further, the requested monitoring reports of the sponsor's representativehave been provided. No further inspections are required.

As requested, also a signed statement that the test product used in the bioequivalence study is identical to the product intended for marketing was provided.

2.4.6. Conclusions on clinical aspects

Based on the presented bioequivalence study Gefitinib Mylan 250 mg film-coated tablets is considered bioequivalent with Iressa 250 mg film-coated tablets by AstraZeneca UK Ltd.

2.5. Risk management plan

Safety concerns

Summary of safety concerns	
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 pregnant or lactating woman • Use in patients with severe renal impairment

The list of safety concerns for Gefitinib Mylan is in line with the one of the reference product.

Pharmacovigilance plan and Risk minimisation measures

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Important identified risks		
Interstitial lung disease	Routine risk minimization measures	Routine pharmacovigilance activities
Hepatitis	Routine risk minimization measures	Routine pharmacovigilance activities

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Gastrointestinal perforation	Routine risk minimization measures	Routine pharmacovigilance activities
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	Routine risk minimization measures	Routine pharmacovigilance activities
Important Potential Risk		
Haemorrhage events (including Gastrointestinal haemorrhage and tumour haemorrhage)	Routine risk minimization measures	Routine pharmacovigilance activities
Cerebrovascular events	Routine risk minimization measures	Routine pharmacovigilance activities
Drug interactions: interactions with oral anticoagulants	Routine risk minimization measures	Routine pharmacovigilance activities
Missing Information		
Use in pregnant or lactating woman	Routine risk minimization measures	Routine pharmacovigilance activities
Use in patients with severe renal impairment	Routine risk minimization measures	Routine pharmacovigilance activities

In line with the reference product, routine pharmacovigilance activities as well as routine risk minimisation activities are sufficient to manage the safety concerns of the medicinal product.

Conclusion

The CHMP and PRAC considered that the risk management plan version 3 is acceptable.

2.6. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Product information

2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet 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.

3. Benefit-risk balance

This application concerns a generic version of Iressa 250 mg film-coated tablet. The reference product Iressa 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.

No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The bioequivalence study forms the pivotal basis with a cross-over design. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Gefitinib Mylan met the protocol-defined criteria for bioequivalence when compared with Iressa. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t},, $AUC_{0-\infty}$, and C_{max} were all contained within the protocol-defined acceptance range of [range, e.g. 80.00 to 125.00%]. Bioequivalence of the two formulations was demonstrated.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the

benefit-risk balance of Gefitinib Mylan is favourable in the following indication:

Gefitinib Mylan 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.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.