Public Assessment Report

Scientific discussion

Erlotinib Apotex 25 mg, 100 mg and 150 mg, film-coated tablets

(erlotinib hydrochloride)

NL/H/3690/001-003/DC

Date: 6 September 2017

This module reflects the scientific discussion for the approval of Erlotinib Apotex 25 mg, 100 mg and 150 mg, film-coated tablets. The procedure was finalised on 22 December 2016. For information on changes after this date please refer to the ‘steps taken after finalisation’ at the end of this PAR.
### List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASMF</td>
<td>Active Substance Master File</td>
</tr>
<tr>
<td>CMD(h)</td>
<td>Coordination group for Mutual recognition and Decentralised procedure for human medicinal products</td>
</tr>
<tr>
<td>CMS</td>
<td>Concerned Member State</td>
</tr>
<tr>
<td>EDMF</td>
<td>European Drug Master File</td>
</tr>
<tr>
<td>EDQM</td>
<td>European Directorate for the Quality of Medicines</td>
</tr>
<tr>
<td>EEA</td>
<td>European Economic Area</td>
</tr>
<tr>
<td>ERA</td>
<td>Environmental Risk Assessment</td>
</tr>
<tr>
<td>GI</td>
<td>Gastro Intestinal</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference of Harmonisation</td>
</tr>
<tr>
<td>IHC</td>
<td>Immunohistochemistry</td>
</tr>
<tr>
<td>ILD</td>
<td>Interstitial Lung Disease</td>
</tr>
<tr>
<td>MAH</td>
<td>Marketing Authorisation Holder</td>
</tr>
<tr>
<td>NSCLC</td>
<td>Non-Small Cell Lung Cancer</td>
</tr>
<tr>
<td>Ph.Eur.</td>
<td>European Pharmacopoeia</td>
</tr>
<tr>
<td>PL</td>
<td>Package Leaflet</td>
</tr>
<tr>
<td>RH</td>
<td>Relative Humidity</td>
</tr>
<tr>
<td>RMP</td>
<td>Risk Management Plan</td>
</tr>
<tr>
<td>SmPC</td>
<td>Summary of Product Characteristics</td>
</tr>
<tr>
<td>TSE</td>
<td>Transmissible Spongiform Encephalopathy</td>
</tr>
</tbody>
</table>
I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Erlotinib Apotex 25 mg, 100 mg and 150 mg, film-coated tablets from Apotex Europe B.V.

The product is indicated for:

Non-Small Cell Lung Cancer (NSCLC):
- The first-line treatment of patients with locally advanced or metastatic NSCLC with Epidermal Growth Factor Receptor (EGFR) activating mutations.
- Switch maintenance treatment in patients with locally advanced or metastatic NSCLC with EGFR activating mutations and stable disease after first-line chemotherapy.
- The treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen.
No survival benefit or other clinically relevant effects of the treatment have been demonstrated in patients with EGFR-IHC negative tumours (see SmPC section 5.1).

Pancreatic cancer:
- in combination with gemcitabine is indicated for the treatment of patients with metastatic pancreatic cancer.
No survival advantage could be shown for patients with locally advanced disease.

When prescribing Erlotinib Apotex, factors associated with prolonged survival should be taken into account (see SmPC sections 4.2 and 5.1). 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 Tarceva 25 mg, 100 mg and 150 mg film-coated tablets which has been registered through centralised procedure (EU/1/05/311/001-003) in the EEA by Roche Registration Limited since 19 September 2005.

The concerned member state (CMS) involved in this procedure was Spain.

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

II. QUALITY ASPECTS

II.1 Introduction

Erlotinib Apotex is a white, round, biconvex film-coated tablet in three strengths:
- The 25 mg strength is engraved with “ER” over “25” on one side and “APO” on the other side.
- The 100 mg strength is engraved with “ER” over “100” on one side and “APO” on the other side.
- The 150 mg strength is engraved with “ER” over “150” on one side and “APO” on the other side.

The product contains as active substance 25 mg, 100 mg or 150 mg of erlotinib, as 27.32 mg, 109.27 or 163.9 mg of erlotinib hydrochloride.

The film-coated tablets are packed in clear PVC/Aclar blisters with aluminum foil.

The excipients are:
*Tablet core* - anhydrous lactose, microcrystalline cellulose (PH 102), croscarmellose sodium, magnesium stearate and colloidal anhydrous silica.
*Tablet coating* - hypromellose 2910 E5, hydroxypropyl cellulose, triethyl citrate and titanium dioxide E171.

The three tablet strengths are dose proportional.
II.2 Drug Substance

The active substance is erlotinib hydrochloride, an established active substance that is not described in a pharmacopoeia. Erlotinib hydrochloride is a white to off-white powder. It is very slightly soluble in water, with its aqueous solubility being dependent on pH with increased solubility at pH less than 5. The active substance has no asymmetric carbons. It exhibits polymorphism. Polymorphic form A is consistently manufactured.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or ‘know-how’ of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The manufacturing process of erlotinib hydrochloride involves three synthesis steps. The active substance is subsequently washed and milled. The drug substance is sufficiently characterised with regard to the chemical structure. The discussion on impurities is sufficient.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. The active substance specification established by the ASMF-holder has been adopted, with additional test and limits for the particle size distribution. Batch analytical data demonstrating compliance with this specification have been provided for three production scale batches.

Stability of drug substance
Stability data on the active substance have been provided for:
- Two pilot scale batches stored at 25°C/60% RH (60 months) and 40°C/75% RH (6 months).
- One scaled up batch stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months).
- Two annual batches stored at 25°C/60% RH (24 months).

No out-of-specification results and no trends have been observed. Based on the data submitted, a retest period could be granted of 60 months when stored at temperatures up to 25°C and protected from exposure to moisture, air and light.

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. Quality by design elements have been applied, resulting in a fixed composition and manufacturing process. No design space is claimed. Pharmaceutical development has been adequately performed.

One bioequivalence study was submitted with the 150 mg strength and the reference product. The products are acceptable in view of composition, manufacture and batch size. Comparative in vitro dissolution tests with the lower strengths at pH 1.2, 4.5 and 6.8 have been performed. The submitted dissolution results support a biowaiver for the 25 mg and 100 mg strength.

Manufacturing process
The drug product is prepared by a conventional dry granulation process followed by compression and film-coating. The process is a standard manufacturing process. It has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for seven pilot scale batches in accordance with the relevant European guidelines.
Control of excipients
The excipients comply with European Pharmacopoeia (Ph.Eur.) 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, average weight, water content, identity, uniformity of dosage units by weight variation, assay, degradation, dissolution and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.
Satisfactory validation data for the analytical methods have been provided. Batch analytical data from seven batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Results of stability studies are provided covering 18 months storage at 25°C/60% RH and 6 months at 40°C/75% RH. No significant changes have been observed. The photostability study demonstrated that the tablets are not sensitive for light. On the basis of the data submitted, a shelf-life was granted of 24 months, without any special storage condition.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate is the only material of animal or human origin included in the drug product. 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 Erlotinib Apotex 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 Erlotinib Apotex 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 Tarceva 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
Erlotinib hydrochloride 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

Bioequivalence study
The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Erlotinib Apotex 150 mg, film-coated tablets (Apotex Europe B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Tarceva 150 mg film-coated tablets (Roche Registered Limited, EU). The submitted bioequivalence study was conducted involving both EU and non-EU reference products (Tarceva from EU and Australia). The assessment for the study focuses on comparison of Erlotinib Apotex with the EU reference product.

The choice of the reference product
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.

Biowaiver
A biowaiver for a bioequivalence study for additional lower strengths (25 mg and 100 mg) of erlotinib is granted:
- The pharmacokinetics for erlotinib are linear.
- All products were manufactured by the same process and the composition of the different strengths is qualitatively the same.
- The proportional amount of excipients is contained in strengths, which is considered acceptable. Thus the composition of the strengths is dose proportional.
- Similarity of dissolution between the lower (25 mg and 100 mg) strengths and 150 mg strength has been demonstrated ($f_2$ calculation).

Design
A monocentric, open label, randomised, three-treatment, three-period, six-sequence, single dose, crossover bioequivalence study was carried out under fasting conditions in 51 healthy male subjects (mean age 34.4 years). Each subject received a single dose (150 mg) of one of the three erlotinib formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were three dosing periods, separated by a washout period of 14 days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1.0, 1.33, 1.67, 2.0, 2.5, 3, 4, 5, 6, 8, 12, 16, 20, 24, 30, 36, 48, 60 and 72 hours after administration of the products.

The design of the study is acceptable. Erlotinib hydrochloride may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of erlotinib hydrochloride. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

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
41 subjects completed all three treatments, and two subjects completed test and European reference treatments. Therefore, 43 subjects were eligible for pharmacokinetic analysis.
Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, \( t_{\text{max}} \) (median, range)) of erlotinib hydrochloride under fasted conditions.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC(_{0-t}) ng.h/ml</th>
<th>AUC(_{0-\infty}) ng.h/ml</th>
<th>C(_{\text{max}}) ng/ml</th>
<th>( t_{\text{max}} ) h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>21918 ± 7138</td>
<td>23527 ± 8782</td>
<td>1225 ± 317</td>
<td>2.0 (0.67 - 4.0)</td>
</tr>
<tr>
<td>Reference</td>
<td>23234 ± 8311</td>
<td>25551 ± 11056</td>
<td>1151 ± 283</td>
<td>2.50 (0.67 - 5.0)</td>
</tr>
<tr>
<td><em>Ratio (90% CI)</em></td>
<td>0.94 (0.90 - 0.98)</td>
<td>0.92 (0.88 - 0.96)</td>
<td>1.05 (0.99 - 1.12)</td>
<td>--</td>
</tr>
</tbody>
</table>

AUC\(_{0-t}\) area under the plasma concentration-time curve from time zero to \( t \) hours

AUC\(_{0-\infty}\) area under the plasma concentration-time curve from time zero to infinity

C\(_{\text{max}}\) maximum plasma concentration

\( t_{\text{max}} \) time for maximum concentration

*In-transformed values

Conclusion on bioequivalence study
The 90% confidence intervals calculated for AUC\(_{0-t}\), AUC\(_{0-\infty}\) and C\(_{\text{max}}\) are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Erlotinib Apotex is considered bioequivalent with Tarceva. 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 Erlotinib Apotex.

Summary table of safety concerns as approved in RMP:

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>Important potential risks</th>
<th>Missing information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous toxicity</td>
<td>None</td>
<td>Pregnancy/lactation</td>
</tr>
<tr>
<td>Interstitial Lung Disease (ILD)</td>
<td></td>
<td>Paediatric population</td>
</tr>
<tr>
<td>Liver injury</td>
<td></td>
<td>Use in patients with severe hepatic impairment</td>
</tr>
<tr>
<td>GI fluid loss</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI perforation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ocular toxicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interaction with potent inducers and inhibitors of CYP3A4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interaction with medicinal products that alter pH of the upper GI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interaction with smoking</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Additional risk minimisation measures are required relating to erlotinib induced ILD. These have been laid down in line with the reference product. It concerns educational material for prescribers to anticipate and manage ILD. The implementation of the additional measures will be agreed at a national level in each of the member states.

IV.4 Discussion on the clinical aspects
For this authorisation, reference is made to the clinical studies and experience with the innovator product Tarceva. 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 Tarceva. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Erlotinib Apotex 25 mg, 100 mg and 150 mg, film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Tarceva 25 mg, 100 mg and 150 mg film-coated tablets. Tarceva 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 Erlotinib Apotex with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 22 December 2016.
### STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE – SUMMARY

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Type of modification</th>
<th>Date of start of the procedure</th>
<th>Date of end of the procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
</tr>
</thead>
</table>
