CBG MEB

Public Assessment Report

Scientific discussion

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

(erlotinib hydrochloride)

NL/H/3820/001-003/DC

Date: 22 May 2018

This module reflects the scientific discussion for the approval of Erlotinib BioOrganics. The procedure was finalised on 24 October 2017. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

AE	Adverse Event
ASMF	Active Substance Master File
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PK	Pharmacokinetics
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 Erlotinib BioOrganics 25 mg, 100 mg and 150 mg, film-coated tablets from BioOrganics BV.

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 it 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, 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) in the EEA by Roche Registration Limited since 19 September 2005.

The concerned member states (CMS) involved in this procedure were Iceland (all strengths), Bulgaria (100 mg, 150 mg) and Romania (100 mg, 150 mg).

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

II. QUALITY ASPECTS

II.1 Introduction

Erlotinib BioOrganics 25 mg is a white, round, biconvex tablet with “E9OB” debossed on one side and “25” on the other.
Erlotinib BioOrganics 100 mg is a white, round, biconvex tablet with a score line on both sides, on one side the tablet is debossed with “E9OB” above the score line and “100” below the score line. The tablet can be divided into equal doses.
Erlotinib BioOrganics 150 mg is a white, round, biconvex tablet with “E9OB” debossed on one side and “150” on the other.

The tablets contain 25 mg, 100 mg or 150 mg erlotinib, as erlotinib hydrochloride.

The film-coated tablets are packed in PVC/Al blisters or oPA/Al/PVC/Al blisters.

The excipients are:
Tablet core - lactose monohydrate, microcrystalline cellulose (E460), sodium starch glycolate, sodium laurilsulfate., magnesium stearate (E470b), cellulose, microcrystalline and calcium hydrogen phosphate, anhydrous.

Tablet coating - hypromellose (E464), hydroxypropylcellulose (E463), titanium dioxide (E171), macrogol

The three strengths are fully 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 yellow powder. It is very slightly soluble in water, with its aqueous solubility being dependent on pH with increased solubility at a pH of 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 all three manufacturers of 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
For each drug substance manufacturer the manufacturing process has been adequately described. The drug substance is sufficiently characterized with regard to the chemical structure. The intended polymorphic form (Form-A) is consistently manufactured.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. A compiled specification covering the tests applied for the active substance from all suppliers is provided. Analytical methods are suitably described and validated.

Stability of drug substance
Manufacturer I
Stability data on the active substance have been provided for three production scale batches stored at 25°C/60% RH (60 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months), one micronized batch stored at 25°C/60% RH (48 months) and three annual batches stored at 25°C/60% RH (12, 24 and 48 months, respectively).
No out-of-specification results and no trends have been observed. The proposed re-test period of 60 months when stored not above 25 °C is justified.

Manufacturer II
Stability data on the active substance have been provided for three batches stored at 25°C/60% RH (60 months) and 40°C/75% RH (6 months). No out-of-specification results and no trends have been observed. The proposed re-test period of 60 months is justified.

Manufacturer III
Stability data on the active substance have been provided for three production scale batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). No out-of-specification results and no trends have been observed. The proposed re-test period of 36 months with no special storage condition is justified.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies were formulation trials, manufacturing process optimization trials and comparative dissolution studies with the innovator product. Control of the morphological form during manufacture and storage of the drug products has been sufficiently discussed. The particle size of the active substance has been discussed, and the proposed

specification for particle size is acceptable. The 100 mg tablet has a score line. Breakability of the tablets has been demonstrated.
The test product (150 mg) used in the bioequivalence study is acceptable in view of composition, manufacture and batch size. The biowaiver for 25 mg and 100 mg is acceptable, based on the provided dissolution profiles which show similar dissolution between the different strengths.

Manufacturing process
The manufacturing process is described as 5 phase process: dry granulation, preparation of the pre-lubricated blend, preparation of the pre-compression blend, compression and film-coating. The process is a standard manufacturing process and has been suitably validated. Three batcher per strength were included in the process validation

Control of excipients
The excipients comply with 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 product specification includes tests for appearance, identification, assay, impurities, dissolution and uniformity of dosage units. The proposed specification is acceptable.
Batch analysis data have been provided of four batches of each strength. The results are consistent and comply.

Stability of drug product
Results of stability studies are available covering 18-36 months storage at 25°C/60% RH and 6 months at 40°C/75% RH. The tablets were packaged in blisters. No significant changes have been observed. A photostability study has been performed in line with the recommendations in ICH Q1B guideline. It has been shown that the drug product is not sensitive to light. Based on the stability results, a shelf-life of 24 months without any special storage conditions has been granted.

Specific measures for 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. A TSE/BSE statement from the manufacturer has been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Erlotinib BioOrganics 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 BioOrganics 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 is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Erlotinib BioOrganics 150 mg, film-coated tablets (BioOrganics BV, the Netherlands) is compared with the pharmacokinetic profile of the reference product Tarceva 150 mg film-coated tablets (Roche Registered Ltd, United Kingdom).

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 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).

Bioequivalence studies
Design
A single-dose, randomised, two-treatment, four-period, replicate design, crossover bioequivalence study was carried out under fasted conditions in 32 healthy male subjects, aged 18-54 years. Each subject received a single dose (150 mg) of one of the 2 erlotinib formulations. The tablet was orally administered with under fasting conditions. There were 4 dosing periods, separated by a washout period of at least 14 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

The design of the conducted bioequivalence study is in accordance with the product specific guidance. The wash-out period is long enough (based on median $t_{1/2}$=36 h, 8 – 10 times the $t_{1/2}$ was applied in order to exclude the PK carry-over effect). The sampling period is long enough which is in accordance with the product specific guidance which points the AUC_{0-72} and C_{max} out as the parameters of interest for the bioequivalence testing. The sampling scheme is adequate to estimate PK parameters (expected t_{max} around 4h). Food might influence the bioavailability of erlotinib. A study under fasting conditions is in accordance with the product specific guidance. In this study a replicate design was chosen, since the MAH expected a highly variable CV_{intra}. Only male subjects were included in this study, because of the risk to women of childbearing potential. Overall, the study design is considered adequate.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
A total of 5 volunteers dropped out (withdrew consent) during this trial. One volunteer only completed the first two periods of the trial and was included in the pharmacokinetic and statistical analyses. Therefore 28 volunteers were subjected to statistical evaluation

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

Treatment N=28	**AUC_{0-72}** ng.h/ml	**$AUC_{0-\infty}$** ng/ml/h	**C_{max}** ng/ml	**Median t_{max}** h
Test	14986 ± 4714	--	1304 ± 351	2.5 (0.5 – 4.5)
Reference	13981 ± 5499	--	1190 ± 386	2.5 (1.0 – 8.0)
***Ratio (90% CI)**	1.07 (1.03 – 1.10)	--	1.10 (1.05 – 1.24)	--
CV_{intra} (%)	25	--	21	--

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

Conclusion on bioequivalence study
No pre-dose plasma levels for erlotinib were detected during the study. AUC_{0-t} / $AUC_{0-\infty}$ < 0.8 occurred in three subjects who received the reference product and one subject receiving the test product.

C_{max} in the first time point occurred in one subject receiving the test product in one period. The MAH was asked to reanalyse the bioequivalence outcome excluding data for this subject. It has been sufficiently demonstrated that exclusion of these data has a minimal effect on the bioequivalence calculation.

The 90% confidence intervals calculated for AUC_{0-72} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Erlotinib BioOrganics 150 mg is considered bioequivalent with Tarceva 150 mg film-coated tablets.

Safety
Regarding safety, no serious adverse events (AEs) were registered during the course of the study. A total of 5 non-serious AEs were registered in 5 volunteers. All of these AEs resulted in full recovery. Three of the AEs were associated to the administration of reference study medication and two were associated with the test study medication.

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 BioOrganics.

- Summary table of safety concerns as approved in RMP

Important identified risks	• Cutaneous toxicity • Gastrointestinal fluid loss • Gastrointestinal perforation • Interaction with medicinal products that alter pH of the upper GI • Interaction with potent inducers and inhibitors of CYP3A4 • Interaction with smoking (CYP1A2 induction) • Interstitial Lung Disease (ILD) • Liver injury • Ocular toxicity
Important potential risks	• None
Missing information	• Paediatric population • Pregnancy/lactation • Use in patients with severe hepatic impairment

Additional risk minimisation measures are required relating to erlotinib induced Interstitial Lung Disease. 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

The package leaflet (PL) has not been evaluated via a user consultation study. A bridging report has been submitted, referring to the approved package leaflet of Tarceva. The differences between the two PLs are considered not to impact readability. Regarding layout, reference is made to successfully user tested leaflets in the house style of the MAH. The bridging report has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Erlotinib BioOrganics 25 mg, 100 mg and 150 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are 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 BioOrganics with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 24 October 2017.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of the procedure	Approval/ non approval	Summary/ Justification for refuse