COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

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

(erlotinib hydrochloride)

NL/H/4179/001-003/DC

Date: 11 February 2020

This module reflects the scientific discussion for the approval of Erlotinib Waverley 25 mg, 100 mg and 150 mg film-coated tablets. The procedure was finalised at 31 October 2019. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Erlotinib Waverley 25 mg, 100 mg and 150 mg film-coated tablets from Reliance Genemedix Ltd.

The product is indicated for:

Non-Small Cell Lung Cancer (NSCLC):

- The first-line treatment of patients with locally advanced or metastatic non- small cell lung cancer (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.
- In patients with tumours without EGFR activating mutations, Erlotinib Waverley is indicated when other treatment options are not considered suitable.
- When prescribing this product, factors associated with prolonged survival should be taken into account.
- No survival benefit or other clinically relevant effects of the treatment have been demonstrated in patients with EGFR-IHC negative tumours.

Pancreatic cancer:

- Erlotinib Waverley 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 Waverley, factors associated with prolonged survival should be taken into account.

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 the United Kingdom.

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

Similarity assessment in view of the orphan drug legislation

The MAH provided a similarity assessment between Erlotinib and Trabedersen, Antroquinonol and Onivyde (nanoliposomal irinotecan). Onivyde has orphan market exclusivity for "Treatment of pancreatic cancer" (based on designation EU/3/11/933) started on 18/10/2016. This orphan market exclusivity will expire on 18/10/2026. Antroquinonol and Traberdersen have no marketing authorisation. The MAH stated that erlotinib is considered not to be similar to Onivyde. The member states agree that Erlotinib Waverley is not similar based on principal molecular structure, mechanism of action and indication. Therefore the orphan status and its juridical and procedural aspects are in this case not an issue.

II. QUALITY ASPECTS

II.1 Introduction

Erlotinib Waverley is a film-coated tablet in three strengths:

- 25 mg: white to off-white, round, biconvex, film-coated tablets, debossed with 'E' upon '25' on one side and plain on the other side.
- 100 mg: white to off-white, round, biconvex, film-coated tablets, debossed with 'E' upon '100' on one side and plain on the other side.
- 150 mg: white to off-white, round, biconvex, film-coated tablets, debossed with 'E' upon '100' on one side and plain on the other side.

The product contains as active substance 25 mg, 100 mg or 150 mg of erlotinib (as erlotinib hydrochloride).

The film-coated tablets are packed in OPA/Al/PVC-Al blisters

The excipients are:
Tablet core - lactose anhydrous, microcrystalline cellulose (E460), sodium starch glycolate Type A, sodium laurilsulfate (E487), colloidal anhydrous silica (E551) and magnesium stearate (E470b)
Tablet coat - hydroxypropyl cellulose (E463), titanium dioxide (E171), sodium laurilsulfate (E487) and hypromellose (E464).

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 the European Pharmacopoeia (Ph.Eur.). It is a white to off-white crystalline powder. Erlotinib hydrochloride is insoluble in water. 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 described manufacturing process of erlotinib hydrochloride involves six stages. Starting materials and drug substance are sufficiently characterised with regard to the chemical structure. No class 1 organic solvents or metal catalysts are used. The intended polymorphic form is consistently manufactured. Acceptable specifications have been adopted for the starting materials, solvents and reagents.

Quality control of drug substance

The active substance specification has been established in-house by the MAH, with additional requirements for particle size and bulk density. The specification is considered adequate to control the quality and acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data for two batches demonstrating compliance with this specification have been provided.

Stability of drug substance

Stability data on the active substance have been provided for three pilot scale batches stored at 25°C/60% RH (48 months) and 40°C/75% RH (6 months) and three additional batches (at least one of full scale) that were stored at 25°C/60% RH (6-48 months). No out-of-specification results and no trends have been observed. Based on the data submitted, a retest period could be granted of 36 months with storage condition: 'Store in a tightly closed container at cool and dry place, temperature not exceeding 25°C' is justified.

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. Drug substance properties with a potential impact on the drug product manufacturability, quality and performance have been discussed and where relevant appropriate controls were implemented. The formulation development started with the characterisation of the reference products. The formulation was optimised with respect to disintegrant concentration, wetting agent concentration and lubricant concentration. Manufacturing process development studies were performed regarding the

blending and compression parameters and film-coating amount. The choices of the packaging and manufacturing process are justified. The choice of the dissolution method for routine control of the drug product is acceptable.
One bioequivalence study was submitted. The test product (150 mg) used in the bioequivalence study is acceptable in view of composition, manufacture and batch size. For the additional strengths a biowaiver is claimed. The biowaiver for the additional strengths 25 mg and 100 mg has been supported by appropriate *in vitro* dissolution data. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The drug product is prepared by dry blending of the components, blending and lubrication, compression and film-coating. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three full-scale batches per strength without debossing and on one full scale batch of each strength with debossing in accordance with the relevant European guidelines.

Control of excipients
The excipients comply with the Ph.Eur. or in-house (film-coating material) requirements. Where relevant functionality related characteristics are controlled. The specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identification, water content, dissolution, assay, related substances, polymorphic form, average weight, uniformity of dosage units, disintegration time and microbial quality. The release and shelf-life requirements are identical. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.
Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three full-scale batches per strength without debossing and on one full scale batch of each strength with debossing from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data have been provided for three full-scale batches of each strength stored at 25°C/60% RH (24 months) and 30°C/65% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in Al-Al blisters (OPA/Al/PVC-Al). No clear trends or changes were seen from the stability results at all storage conditions and no differences were observed between the different storage conditions. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. On basis of the data submitted, a shelf life was granted of 2 years without special storage conditions.

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 Waverley 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 Waverley 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 one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Erlotinib Waverley 150 mg film-coated tablets (Reliance Genemedix Ltd, UK) is compared with the pharmacokinetic profile of the reference product Tarceva 150 mg film-coated tablets (Roche registration Ltd, Germany).

The choice of the European 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

For the additional lower strengths of 25 mg and 100 mg a biowaiver is granted, based on the following:

- All products were manufactured by the same process
- The composition of the different strengths is qualitatively the same
- The composition of the strengths is dose proportional
- Comparable dissolution of the 25 mg and 150 mg strengths, at three pH's, has been shown.

Bioequivalence study

Design

An open label, randomised, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study was carried out under fasted conditions in 40 healthy male subjects, aged 19-44 years. Each subject received a single dose (150 mg) of one of the two erlotinib formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were two dosing periods, separated by a washout period of 10 days.

Blood samples were collected pre-dose and at 0.25, 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 3.33, 3.67, 4.00, 4.33, 4.67, 5.00, 5.50, 6.00, 7.00, 9.00, 12.00, 16.00, 24.00, 36.00, 48.00, 60.00, 72.00 hours after administration of the products.

The design of the study is acceptable. The 10 day wash-out period is considered sufficient.

Analytical/statistical methods

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

Results

One subject did not report for the second period check-in and one subject was withdrawn due to an adverse event. Therefore, a total of 38 subjects completed the study and were eligible for pharmacokinetic analysis.

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

Treatment N=38	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	25102 ± 7391	--	1452 ± 469	2.0 (0.5-24)
Reference	27778 ± 7914	--	1514 ± 395	2.25 (1.0-4.33)
***Ratio (90% CI)**	0.90 (0.83 – 0.98)	--	0.93 (0.85 – 1.02)	--
$AUC_{0-\infty}$ 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				

**ln-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Erlotinib Waverley 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 Waverley.

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

Important identified risks	None
Important potential risks	None
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient.

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 been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of: a pilot test with 4 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Erlotinib Waverley 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 Waverley with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 31 October 2019.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

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