COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Erlotinib SUN 25 mg, 100 mg, 150 mg, film-coated tablets

(erlotinib hydrochloride)

NL/H/4092/001-003/DC

Date: 15 August 2019

This module reflects the scientific discussion for the approval of Erlotinib SUN 25 mg, 100 mg, 150 mg film-coated tablets. The procedure was finalised at 18 January 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
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 SUN 25 mg, 100 mg and 150 mg, film-coated tablets from SUN Pharmaceutical Industries 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 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 SUN is indicated when other treatment options are not considered suitable.

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:

- Erlotinib SUN 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 SUN, 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 states (CMS) involved in this procedure were Germany, Spain, Italy, Poland, Romania, and the United Kingdom.

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

Similarity assessment

The MAH has compared the product with the authorized orphan medicinal products Onivyde and SomaKit TOC in the context of similarity. Onivyde has orphan market exclusivity for "Treatment of pancreatic cancer" (EU/3/11/933) started on 18/10/2016. SomaKit TOC has orphan market exclusivity for "Diagnosis of gastro-entero-pancreatic neuroendocrine tumours" (EU/3/15/1450) started on 12/12/2016. The MAH showed that erlotinib is not similar to Onivyde and SomaKit TOC. This is acceptable. Therefore the orphan status and its juridical and procedural aspects are in this case not an issue.

II. QUALITY ASPECTS

II.1 Introduction

Erlotinib SUN is a white to off white round biconvex film coated tablet in three strengths debossed with "RL" on one side:
25 mg –and "11" on other side.
100 mg - and "12" on other side.
150 mg - and "13" on 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 tablet is packed in OPA/Al/HDPE/PE+Desiccant/HDPE/PE/Al blisters or HDPE bottles with child-resistant cap and induction seal liner, containing silica gel.

The excipients are:
Tablet core - lactose monohydrate, microcrystalline cellulose (E460), sodium starch glycolate (type A), sodium lauryl sulphate and magnesium stearate (E470b)
Film coating (Opadry White (YS-1-7040)) - hypromellose (E464), macrogol 8000, titanium dioxide (E171) and talc

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 any Pharmacopoeia. Erlotinib hydrochloride 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. Form-A is used.

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 three synthetic, one purification and one salt formation step. The active substance is then dried and may be micronized. The drug substance is sufficiently characterized with regard to the chemical structure. The polymorphic form is consistently manufactured and suitably controlled in the active substance specification. The impurities have adequately been discussed.

Quality control of drug substance

The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for six batches.

Stability of drug substance

Stability data on the active substance have been provided for three production scale batches and three up-scale batches stored at 25°C/60% RH (up to 60 months) and 40°C/75% RH (up to 6 months) and one micronized batch stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 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 without special storage conditions.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The main development studies were formulation trials, manufacturing process optimization trials and comparative dissolution studies with the innovator product. 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 has been adequately justified based on comparative *in vitro* dissolution data. The pharmaceutical development of the products has been adequately performed.

Manufacturing process

The drug product is prepared by conventional dry granulation process followed by compression and film-coating. The process is a standard manufacturing process. The manufacturing process has been adequately validated according to relevant European guidelines although questions on sampling are raised. Process validation data on the product have been presented for three production scaled batches in accordance with the relevant European guidelines.

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 specification includes tests for description, identification, average weight, water content, uniformity of dosage units, assay, impurities, dissolution and microbial purity. Test and acceptance criteria for the dimensions (thickness, diameter) of the film-coated tablets have been included in release and shelf-life specification. 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 four batches of each strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Results of stability studies have been provided covering 24 months storage at 25°C/60% RH and six months at 40°C/75% RH on three full scaled batches per strength. The batches were stored in the proposed commercial blister and HDPE bottles. No significant changes have been observed in any of the tested parameters during storage. Results of a photostability study in accordance with ICH Q1B have been presented showing that the drug product is not sensitive to light exposure. Based on the data submitted, a shelf-life of two years without any special storage requirements is granted.

In use studies have been performed over a study period of 30 days for the HDPE bottles stored at 25°C/60% RH. No clear trends or changes were seen in any of the tested parameters. Based on the results of these studies the claimed in-use shelf of 30 days after first opening of the bottles is justified.

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 SUN 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 SUN 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

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Erlotinib SUN 150 mg film-coated tablets (Sun Pharmaceutical Industries Limited, country) is compared with the pharmacokinetic profile of the reference product Tarceva 150 mg film-coated tablets (Roche Pharma AG, Germany).

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

The MAH applied for a biowaiver for the lower strengths 25 mg and 100 mg. The following conditions are fulfilled:

- The pharmaceutical products are manufactured by the same manufacturer and process
- The qualitative composition of different strengths is the same
- The composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance is the same for all strengths since MAH's 25 mg, 100 mg and 150 mg strengths are scale up/scale down strengths.
- Appropriate *in vitro* dissolution data available.

  Dissolution data have been generated on the three product strengths in pH 1.2, pH 4.5 and pH 6.8 media without a surfactant.

  In pH 6.8 medium f2-calculation or bootstrapping was not possible due to the very poor dissolution (<15% after 60 minutes) and high % RSD values. In this medium similarity was concluded by the MAH based on visual comparison and comparison of the dissolution profiles of the respective reference product strengths showing the same poor dissolution.

  In pH 4.5 and pH 1.2 dissolution media f2-calculation was not possible due to too high % RSD values. Higher RSD values in pH 4.5 and pH 1.2 media are because of cone formation in the dissolution vessels at 900 ml and 50 rpm, without surfactant. For the comparison in pH 4.5 and pH 1.2 media bootstrapping was performed. In both pH mediums similarity is demonstrated by bootstrap for 100 mg vs 150 mg and 6x 25 mg vs 150 mg.

Based on these data the biowaiver for the 25 mg and 100 mg additional strengths is considered justified.

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 48 healthy male and female subjects, aged 20-44 years. Each subject received a single dose (150 mg) of one of the two erlotinib hydrochloride formulations. The tablet was orally administered after an overnight fast of at least ten hours. There were two dosing periods, separated by a washout period of 14 days.

Blood samples were collected within one hour before dosing and at 0.17, 0.3, 0.5, 0.8, 1.0, 1.3, 1.7, 2.0, 2.3, 2.7, 3.0, 3.3, 3.7, 4.0, 4.3, 4.7, 5.0, 6.0, 8.0, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable.

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

Results
Two subjects dropped out (both before the second period) because of personal situation changes at home or work and two subjects were withdrawn from the study (during or after period 1) because of adverse events (rash in both cases). Therefore 44 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=44	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)
Test	18990 ± 6887	20218 ± 7274	1011 ± 406	2.4 ± 1.1
Reference	18211 ± 5936	19490 ± 6385	907 ± 335	3.0 ± 1.2
***Ratio (90% CI)**	1.04 (0.97 – 1.11)	1.02 (0.95 – 1.10)	1.11 (1.02 – 1.20)	--
$AUC_{0-\infty}$ 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}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Erlotinib SUN 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 SUN.

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

Important identified risks	• Cutaneous toxicity • Interstitial lung disease (ILD) • Liver injury • Gastrointestinal fluid loss • Gastrointestinal perforation • Ocular toxicity • Interaction with potent inducers and inhibitors of CYP3A4 • Interaction with medicinal products that alter pH of the upper GI tract • Interaction with smoking (CYP1A2 induction)
Important potential risks	--
Missing information	• Pregnancy/lactation • Paediatric population • Use in patients with severe hepatic impairment

In line with the risk minimisations of Tarceva, the MAH proposed educational material for healthcare professionals for risk of erlotinib-induced ILD, which is accepted. The educational material should contain the following key elements:

- Indications of erlotinib;
- ILD-like events, including fatalities, have been reported uncommonly in patients receiving erlotinib;
- Information on the incidence (overall incidence of approximately 0.6%); higher incidence of ILD (approximately 5% with a mortality rate of 1.5%) is seen among patients with Japanese origin;
- Information on confounding or contributing factors (concomitant or prior chemotherapy, prior radiotherapy, pre-existing parenchymal lung disease, metastatic lung disease, or pulmonary infections);
- Management of ILD-like events;
- In patients who develop acute onset of new and/or progressive unexplained pulmonary symptoms such as dyspnoea, cough and fever, erlotinib should be interrupted pending diagnostic evaluation;
- Patients treated concurrently with erlotinib and gemcitabine should be monitored carefully for the possibility to develop ILD-like toxicity;
- If ILD is diagnosed, the product should be discontinued and appropriate treatment initiated as necessary.

The full text of the education material and the requirements for distribution will be assessed at national level.

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 three participants, followed by two rounds with ten 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 SUN 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 SUN with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 18 January 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