COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

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

(erlotinib hydrochloride)

NL/H/4407/001-003/DC

Date: 15 October 2019

This module reflects the scientific discussion for the approval of Erlotinib Xiromed 25 mg, 100 mg and 150 mg film-coated tablets. The procedure was finalised at 20 March 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 Xiromed 25 mg, 100 mg and 150 mg film-coated tablets from Medical Valley Invest AB.

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 Xiromed 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.

Pancreatic cancer:

- Erlotinib Xiromed 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 Xiromed, 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 states (CMS) involved in this procedure were Germany, Denmark, Norway and Sweden.

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 versus the authorised orphan medicinal product Onivyde in the context of similarity. Onivyde has orphan market exclusivity for "Treatment of pancreatic cancer" (based on designation EU/3/11/933) started on 18/10/2016. The MAH stated that erlotinib is considered not to be similar to Onivyde. The member states agree that Erlotinib Xiromed 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 Xiromed is a film-coated tablet in three strengths:

- 25 mg film-coated tablets are white, round, biconvex tablets with 'H' on one side and '28' on the other side.
- 100 mg film-coated tablets are white, round, biconvex tablets with 'H' on one side and '21' on the other side.
- 150 mg film-coated tablets are white, round, biconvex tablets with 'H' on one side and '22' on the other side.

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

The film-coated tablets are packed in OPA/Alu/PVC - Alu blisters and/or white opaque high density polyethylene (HDPE) bottles with a white opaque polypropylene ribbed child-resistant closure, silica gel sachet and purified cotton.

The excipients are:
Tablet core - lactose monohydrate, microcrystalline cellulose (E460), sodium starch glycolate Type A, sodium laurilsulfate and magnesium stearate (E470b).
Tablet coat - hydroxypropyl cellulose (E463), titanium dioxide (E171), macrogol 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 any Pharmacopoeia (Ph.Eur.). It is a white or off-white crystalline powder. 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. 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 five steps. Starting materials and drug substance are sufficiently characterised 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. The specification included tests for particle size distribution and microbial quality. Batch analytical data demonstrating compliance with this specification have been provided for four batches.

Stability of drug substance

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),
- one annual batch 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 25°C.

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 optimisation trials and comparative dissolution studies with the innovator product.

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. Sufficient information has been provided to accept the biowaiver of strengths for the 25 mg and 100 mg strengths.

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 validated according to relevant European guidelines. Process validation data on the product have been presented for three 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, resistance to crushing, water content, uniformity of dosage units, dissolution, impurities, assay, microbiological examination, and identification of colorant. 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 batches of each strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three batches of each strength. Tablets were stored in the proposed packages. Results of stability studies are available covering 24 months storage at 25°C/60% RH and 6 months at 40°C/75% RH. Except for a decrease in water content at both stability conditions initially, no significant changes have been observed.

A photostability study has been done in line with the ICH Q1B Note for guidance on the photostability testing of new active substances and medicinal products. The tablets are photo-stable and no protection from light is considered required.

On basis of the data submitted, a shelf life was granted of 24 months 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 Xiromed 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 Xiromed 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

Xiromed 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 Xiromed 150 mg film-coated tablets (Medical Valley Invest AB, Sweden) 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.

Similarity of the dissolution profiles of the 100 mg versus 150 mg in two pH's (0.1N HCl and acetate buffer pH 4.5) has been demonstrated. Due to the very poor release in pH 6.8 medium and the high RSD values, no statistical calculation could be applied for the comparison of the 100 mg strength with the 150 mg strength. It has been subsequently adequately shown that poor dissolution in pH 6.8 is drug substance related, and not a result of the drug product formulation.

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 56 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 0.5, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.33, 4,67, 5, 5.5, 6, 7, 8, 10, 12, 16, 24, 36, 48, 72 and 96 hours after administration of the products.

The design of the study is acceptable. The 10 day wash-out period is considered sufficient. In contrast to the product-specific guidance, samples were taken until 96 hours, whereas 72 hours is considered sufficient. This is not expected to affect the outcome of the study.

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 were withdrawn from the study on medical grounds and three subjects discontinued from the study on their own accord. Therefore, 51 subjects 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=51	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	16841 ± 5273	17070 ± 5283	1516 ± 497	2.67 (1.0 - 24)
Reference	17327 ± 6292	17525 ± 6367	1438 ± 501	2.67 (1.0 - 7.0)
***Ratio (90% CI)**	1.01 (0.90 – 1.12)	1.01 (0.91 – 1.12)	1.09 (0.96 – 1.23)	--

$AUC_{0-\infty}$ 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
$t_{1/2}$ half-life
CV coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC0-t, AUC0-∞ and Cmax are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Erlotinib Xiromed 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 Xiromed.

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 for the risks and areas of missing information.

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 Xiromed 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 Xiromed with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 20 March 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