COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Fokleros 100 mg and 150 mg, film-coated tablets (erlotinib (as hydrochloride))

NL/H/5295/001-002/MR

Date: 20 February 2023

This module reflects the scientific discussion for the approval of Fokleros 100 mg and 150 mg, film-coated tablets. The procedure was finalised at 22 March 2022. 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
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
IHC	Immunohistochemistry
MAH	Marketing Authorisation Holder
MRP	Mutual recognition procedure
NSCLC	Non-small cell lung cancer
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of medicinal 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 Fokleros 100 mg and 150 mg, film-coated tablets from Synthon B.V.

The product is indicated for:

- Non-small cell lung cancer (NSCLC)
  - for the first-line treatment of patients with locally advanced or metastatic NSCLC with epidermal growth factor receptor (EGFR) activating mutations
  - for switch maintenance treatment in patients with locally advanced or metastatic NSCLC with EGFR activating mutations and stable disease after first-line chemotherapy
  - for 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, when other treatment options are not considered suitable.

  When prescribing Fokleros, 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-immunohistochemistry (IHC) negative tumours.

- Pancreatic cancer
  - in combination with gemcitabine, for the treatment of patients with metastatic pancreatic cancer.

  When prescribing Fokleros, factors associated with prolonged survival should be taken into account. No survival advantage could be shown for patients with locally advanced disease.

A comprehensive description of the indications and posology is given in the SmPC.

The innovator product is Tarceva 100 mg and 150 mg film-coated tablets (EU/1/05/311/002-003) by Roche Registration GmbH, registered centrally in the EEA since 19 September 2005.

This current product has been approved via a mutual recognition procedure (MRP). The national marketing authorisations for Erlotinb Synthon 100 mg (RVG 123051) and 150 mg film-coated tablets (RVG 123052) were granted on 30 May 2018 in the Netherlands. During this MRP, the product name was changed from 'Erlotinib Synthon 100/150 mg, film-coated tablets' to 'Fokleros 100/150 mg, film-coated tablets'.

The concerned member states (CMS) involved in this procedure were Bulgaria, Hungary, Romania and Slovenia.

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

Similarity assessment

The MAH has provided a similarity report due to potential similarity with an authorised orphan medicinal product under market exclusivity. Having considered the arguments presented by the MAH and with reference to Article 8 of Regulation (EC) No 141/2000, Fokleros was considered not similar (as defined in Article 3 of Commission Regulation (EC) No. 847/2000) to Onivyde pegylated liposomal 4.3 mg/ml concentrate for dispersion for infusion (irinotecan). Reasons included differences in the indications, molecular structure of the substances and methods of action. Therefore, with reference to Article 8 of Regulation (EC) No. 141/2000, the existence of any market exclusivity for Onivyde pegylated liposomal 4.3 mg/ml concentrate for dispersion for infusion (irinotecan) in the treatment of pancreatic cancer, did not prevent the granting of the marketing authorisation of Fokleros. This finding was without prejudice to the outcome of the scientific assessment of the marketing authorisation application.

II. QUALITY ASPECTS

II.1 Introduction

Fokleros 100 mg, film-coated tablets are white, round, biconvex tablets 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.
Fokleros 150 mg, film-coated tablets are white, round, biconvex tablets with “E9OB” debossed on one side and “150” on the other.

One film-coated tablet contains as active substance 100 mg or 150 mg erlotinib (as erlotinib hydrochloride), corresponding to 109.28 mg and 163.92 mg erlotinib hydrochloride, respectively.

The two tablet strengths are dose proportional.

The tablets are packed in oriented polyamide (oPA)/Aluminium/PVC/Aluminium blisters.

The excipients are:
Tablet core – lactose monohydrate, (microcrystalline and calcium hydrogen phosphate anhydrous) cellulose, sodium starch glycolate, colloidal anhydrous silica, microcrystalline cellulose (E460), sodium lauryl sulphate and magnesium stearate (E470 b).
Tablet coating – hypromellose (E464), hydroxypropyl cellulose (E463), titanium dioxide (E171) and macrogol.

II.2 Drug Substance

The active substance is erlotinib hydrochloride, an established active substance not described in any pharmacopoeia. Erlotinib hydrochloride is very slightly soluble in water, with its aqueous solubility being dependent on pH, with increased solubility at a pH<5. The

active substance has no asymmetric carbons. It exhibits polymorphism and form A is consistently 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

For each of the three drug substance manufacturers, the manufacturing process has been adequately described. For all three, the drug substance is 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. A compiled specification covering the tests 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 micronised 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 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 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. The main development studies were formulation

trials, manufacturing process optimisation trials and comparative dissolution studies with the innovator product. Control of the morphological form during manufacture and storage of the drug product has been sufficiently discussed. The particle size of the active substance has been discussed, and the proposed specification for particle size is acceptable. The test product (150 mg) used in the bioequivalence study is acceptable in view of composition, manufacture and batch size. The biowaiver for 100 mg is acceptable, based on the provided dissolution profiles.

Manufacturing process

The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for at least three batches per strength of both manufacturing sites, in accordance with the relevant European guidelines. The drug product is prepared by a conventional dry granulation process followed by compression and film-coating. The process is a standard manufacturing process and has been suitably validated for both manufacturing sites.

Control of excipients

The quality of the excipients is sufficiently described and 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 appearance, identification, assay, impurities, dissolution and uniformity of dosage units. 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 analysis 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 from four batches of each strength, in accordance with applicable European guidelines. The stability studies cover 36 months storage at 25°C/60% RH and 6 months at 40°C/75% RH. No significant changes have been observed. Photostability studies have been performed on one batch of each strength. The tablets were exposed to daylight and UV light for 3 days. As no significant changes in assay, impurities, dissolution and water content were observed between the untreated (dark control) and directly exposed product, the product is regarded as photo stable. On basis of the data submitted, a shelf life was granted of 3 years. No specific storage conditions need to be included in the SmPC or on the label.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

For lactose, 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. There are no other substances of animal origin present in the product nor have any been used in the manufacturing of this product.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Fokleros 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 Fokleros 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 besides the bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Fokleros 150 mg, film-coated tablets (Synthon B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Tarceva 150 mg film-coated tablets (Roche Registration GmbH, Germany).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

The MAH has requested a biowaiver of strengths for Fokleros 100 mg, film-coated tablets, based on the bioequivalence study with the 150 mg tablet. The requirements for such a biowaiver are met: the qualitative composition of the 100 mg and 150 mg strengths is the same and the composition of the strengths is quantitatively dose-proportional. The 100 mg tablet is manufactured by the same process as the 150 mg tablets and has comparable dissolution profiles to the 150 mg tablet according to the provided *in vitro* dissolution data. The choice of the highest strength to be used in the bioequivalence study is in line with the EMA product specific bioequivalence guideline. Consequently, the requested biowaiver for the 100 mg strength was deemed acceptable.

Bioequivalence study

Design

An open label, randomised, single dose, four-period, replicate, 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 two erlotinib formulations. The tablet was orally administered with 240 mL water after an (overnight) fast from 9 PM the night before dosing, until lunch time (at least 4 hours post dose). There were four 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 fasting conditions are in accordance with the EMA product specific guidance (the tablets are taken at least one hour before or two hours after the ingestion of food). 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. 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

A total of five subjects dropped out (by withdrawing consent) during this trial. One of these subjects completed the first two periods of the trial and was included in the analysis. Therefore, a total of 28 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=28	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	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 – 1.20)	--	1.10 (1.05 – 1.24)	--

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t. AUC_{0-72h} can be reported instead of AUC_{0-t}, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products.
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time. $AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}
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 performed bioequivalence study, Fokleros 150 mg, film-coated tablets is considered bioequivalent with Tarceva 150 mg film-coated tablets. The results of the bioequivalent study could be extrapolated to the lower strength, so a biowaiver was granted for Fokleros 100 mg, film-coated tablets.

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 Fokleros.

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 apart from the bioequivalence study. The MAH demonstrated through this bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the 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 (EU/1/05/311/002-003). 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

Fokleros 100 mg and 150 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Tarceva 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 Fokleros with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finalised with a positive outcome on 22 March 2022.

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
NL/H/5295/1-2/IA/001/G	To delete manufacturers responsible for batch release	Yes	24-8-2022	Approved	N/A
NL/H/5295/1-2/R/001	Renewal	No	28-10-2022	Approved	N/A