COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Lapatinib Biogaran 250 mg, film-coated tablets (lapatinib ditosylate monohydrate)

NL/H/5466/001/DC

Date: 07 October 2022

This module reflects the scientific discussion for the approval of Lapatinib Biogaran 250 mg, film-coated tablets. The procedure was finalised at 3 July 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
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 Lapatinib Biogaran 250 mg, film-coated tablets, from Biogaran.

The product is indicated for the treatment of adult patients with breast cancer, whose tumours overexpress HER2 (ErbB2);

- in combination with capecitabine for patients with advanced or metastatic disease with progression following prior therapy, which must have included anthracyclines and taxanes and therapy with trastuzumab in the metastatic setting (see section 5.1 of the SmPC);

- in combination with trastuzumab for patients with hormone receptor-negative metastatic disease that has progressed on prior trastuzumab therapy(ies) in combination with chemotherapy (see section 5.1 of the SmPC);

- in combination with an aromatase inhibitor for postmenopausal women with hormone receptor positive metastatic disease, not currently intended for chemotherapy. The patients in the registration study were not previously treated with trastuzumab or an aromatase inhibitor (see sections 4.4. and 5.1 of the SmPC). No data are available on the efficacy of this combination relative to trastuzumab in combination with an aromatase inhibitor in this patient population.

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 Tyverb 250 mg film-coated tablets which has been registered in the EEA via the centralised procedure since 10 June 2008 (EU/1/07/440) by Novartis Europharm Limited.

The concerned member state (CMS) involved in this procedure was France.

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

II. QUALITY ASPECTS

II.1 Introduction

Lapatinib Biogaran is an oval, biconvex, off-white film-coated tablet debossed with "250" on one side and plain on the other and contains as active substance lapatinib ditosylate monohydrate, equivalent to 250 mg lapatinib.

The tablets are packed in foil blisters (Aluminium-OPA/Alu/PVC).

The excipients are:
Tablet core – cellulose, microcrystalline (type 101, E460), povidone K30 (E1201), sodium starch glycolate (Type A) and magnesium stearate (E470b);
Tablet coating – hypromellose 2910 (3 mPa·s and 6 mPa·s, E464), titanium dioxide (E171), macrogol 400 (E1521), polysorbate 80 (E433) and yellow iron oxide (E172).

II.2 Drug Substance

The active substance is lapatinib ditosylate monohydrate, an established active substance not described in any pharmacopoeia. The substance is an achiral, yellow to yellow-green crystalline powder. It exists as a monohydrate polymorphic form, only a single monohydrate form is reported in the literature.

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 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 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.

<u>Manufacturing process</u>
The manufacturing process consists of three steps, with four starting materials, three synthetic intermediates (one non-isolated) and an isolated crude active substance. Detailed discussion was provided for impurities controlled in the intermediates, accompanied with batch data, including how well impurities are purged in the final purification step. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised.

<u>Quality control of drug substance</u>
The active substance specification is considered adequate to control the quality and is in line with ICH guidelines. Batch analytical data demonstrating compliance with this specification have been provided for four batches. Drug substance specification includes tests for

description, identification, water content, sulphated ash, related substances, genotoxic impurity, assays, and residual solvents, polymorphism, and microbiological examination. The active substance manufacturer specifies eight impurities with the related substances method and an extra (repeated) purification step has been introduced by the MAH to ensure all impurities meet the limit. The active substance is a tosylate and the manufacturer has investigated potential formation of ester tosylates (methyl and ethyl) and neither are formed. A proper risk assessment was provided by the active substance manufacturer on potential formation of nitrosamines and there is no identified nitrosamine risk.

Stability of drug substance

Stability data on the active substance have been provided for three batches as per current ASMF in accordance with applicable European guidelines demonstrating the stability of the active substance for 24 months at 30°C at both 65% and 75% RH. Based on the data submitted, a retest period could be granted of 24 months. This drug substance does not require any storage temperature conditions, but should be preserved in well-closed containers and protected from light as photosensitivity was shown during forced degradation.

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 have been explained. The trials and results are summarised, supporting the selected manufacturing process. Dissolution at three pHs and in the quality control medium was found sufficient in both the finished product and in the test product used in the bioequivalence studies. The MAH has given a thorough discussion on the development of the dissolution procedure. The choice of packaging is justified. Overall, the pharmaceutical development of the product has been adequately described.

Manufacturing process

The manufacturing process has been validated according to relevant European guidelines and consists of dispensing, granulation, blending, compression, film-coating and packaging. The proposed batch size is acceptable. The product is manufactured using conventional manufacturing techniques and process validation data on the product has been presented for two full scale batches.

Control of excipients

The excipients comply with Ph. Eur. requirements where possible and the presented data for the non-Ph. Eur. method is also adequate. 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 of lapatinib, tosylates, assay, related substances, dissolution, uniformity of mass, uniformity of dosage

units, dimensions, identification of titanium dioxide and of iron oxide, and microbiological examination. The release and shelf-life limits are identical, except for one impurity where a tighter limit has been adopted at release to allow a slight increase during shelf-life. 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 two full scale batches and one pilot scale batch 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 on one pilot scaled batch and two production scaled batches stored at 25°C/60% RH (18 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in Aluminium-OPA/Alu/PVC blisters or High-Density Polyethylene (HDPE) bottles. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. No clear trends or out-of-specifications results are observed at any condition, except for an increase in one impurity. This impurity remains within specification at both storage conditions although it rises more at accelerated conditions. The MAH has performed a 3 month in-use stability study for the HDPE bottle packaging in which no out-of-specification results were recorded. The only trend observed was an increase in the impurity, which was similar to that observed in the regular stability studies. Hence, there is no need to adopt an in-use shelf-life. The proposed shelf-life of 30 months without special storage conditions is acceptable.

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

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Lapatinib Biogaran 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 Lapatinib Biogaran 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 Tyverb 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

Lapatinib is a well-known active substance with established efficacy and safety. 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 performed two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test product Lapatinib 250 mg, film-coated tablets, (Biogaran, France) is compared with the pharmacokinetic profile of the reference product Tyverb 250 mg film-coated tablets (Novartis Europharm Limited, Ireland). The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

According to the SmPC, Lapatinib Biogaran should be taken either at least one hour before or at least one hour after food. Both a fasted and a semi-fed study were conducted.

Bioequivalence studies

Study 1 – fasting, single dose, 250 mg

Design

An open label, balanced, single-dose, randomised, four-period, two-treatment, two-sequence, fully replicate, crossover bioequivalence study was carried out under fasted conditions in 64 healthy male subjects, aged 18-41 years. Each subject received a single dose (250 mg) of one of the two lapatinib formulations in each of the four periods. The tablets were orally administered with approximately 240 mL water after an overnight fast of 10 hours. There were four dosing periods, separated by a washout period of 8 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, 8.00, 12.00, 16.00, 24.00, 36.00, 48.00 and 72.00 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

Five subjects withdrew from the study: two subjects withdrew consent and three subjects failed to report to the clinical study site. This resulted in 59 subjects completing the study. Partial data of withdrawn subjects were used, which resulted in 63 participants being included in the statistical analysis.

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

Treatment N=63	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)
Test	7283 ± 3251	7566 ± 3356	461 ± 203	4.33 (2.5 – 7.0)
Reference	7705 ± 3300	8003 ± 3415	481 ± 214	4.33 (2.5 – 6.0)
***Ratio (90% CI)**	0.95 (0.89 – 1.01)	--	0.97 (0.91 – 1.04)	--

$AUC_{0-\infty}$	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

Study 2 – semi-fed, single dose, 250 mg

Design

An open label, balanced, single-dose, randomised, four-period, two-treatment, two-sequence, fully replicate, crossover bioequivalence study was carried out under semi-fed conditions in 64 healthy male subjects, aged 18-44 years. Each subject received a single dose (250 mg) of one of the two lapatinib formulations. The tablet was orally administered with 240 mL water after an overnight fast for at least 10 hours before the intake of a high-fat, high calorie (946 kcal) breakfast 60 minutes before dosing, which was consumed completely within 30 minutes. The breakfast consisted of: milk, sugar, egg, onion, oil, chicken, bread, butter and potatoes. There were four dosing periods, separated by a washout period of 14 days. According to the SmPC, Lapatinib Biogaran should be taken either at least one hour before or at least one hour after food. Therefore, the semi-fed conditions of this study are in line with the bioequivalence guideline.

Blood samples were collected pre-dose and at 1.00, 1.50, 2.00, 2.50, 3.00, 3.33, 3.67, 4.00, 4.33, 4.67, 5.00, 5.33, 5.67, 6.00, 6.50, 7.00, 8.00, 12.00, 16.00, 24.00, 36.00, 48.00 and 72.00 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 reasons for re-analysis are acceptable and were prespecified in the protocol and the reproducibility of the results and robustness of the assay are considered acceptable. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

Seven subjects withdrew from the study: one subject withdrew consent (period 3), four subjects failed to report to the clinical study site, one subject vomited during period 1 and one subject did not completely consume the breakfast in period 3. This resulted in 57 subjects completing the study. Because partial data were used from withdrawn subjects, this led to 62 subjects being included in the statistical analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of lapatinib under semi-fed conditions.

Treatment N=62	**AUC_{0-t} (ng.h/ml)**	**$AUC_{0-\infty}$ (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	12457 ± 3800	12816 ± 3970	863 ± 223	4.67 (2.0 – 7.0)
Reference	12863 ± 4084	13235 ± 4297	900 ± 221	4.67 (1.5 – 7.0)
***Ratio (90% CI)**	0.97 (0.94 – 1.00)	--	0.95 (0.92 – 0.98)	--

$AUC_{0-\infty}$	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 studies

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 studies Lapatinib Biogaran is considered bioequivalent with Tyverb.

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 Lapatinib Biogaran.

Table 3. Summary table of safety concerns as approved in RMP

Important identified risks	• Hepatobiliary events • Decreased left ventricular ejection fraction (LVEF) • Pneumonitis/Interstitial lung disease (ILD) • Interactions with other drugs • QTc prolongation • Severe cutaneous reactions • Food effect
Important potential risks	• None
Missing information	• Elderly • Pregnant or lactating females

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 Tyverb. 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 has been performed on the basis of a bridging report making reference to Tyverb 250 mg film-coated tablets (EMA/H/C/795/II/0004) for the content and to Felocord 5 mg and 7.5 mg film-coated tablets (HU/H/0448/001-002/DC) for the design and layout. 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

Lapatinib Biogaran 250 mg, film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Tyverb 250 mg film-coated tablets. Tyverb 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 Lapatinib Biogaran with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 3 July 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
N/A	N/A	N/A	N/A	N/A	N/A