CBG MEB

Public Assessment Report

Scientific discussion

Imatinib Koanaa 100 mg and 400 mg film-coated tablets

(imatinib mesilate)

NL/H/3510/001-002/DC

Date: 21 December 2017

This module reflects the scientific discussion for the approval of Imatinib Koanaa 100 mg and 400 mg film-coated tablets. The procedure was finalised on 21 September 2016. 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
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 Imatinib Koanaa 100 mg and 400 mg film-coated tablets from Koanaa Healthcare Limited.

The product is indicated for:

- Paediatric patients with newly diagnosed Philadelphia chromosome (bcr-abl) positive (Ph+) chronic myeloid leukaemia (CML) for whom bone marrow transplantation is not considered as the first line of treatment.
- Paediatric patients with Ph+ CML in chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis.
- Adult patients with Ph+ CML in blast crisis.
- Adult and paediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) integrated with chemotherapy.
- Adult patients with relapsed or refractory Ph+ ALL as monotherapy.
- Adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements.
- Adult patients with advanced hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL) with FIP1L1-PDGFRα rearrangement.

The effect of imatinib on the outcome of bone marrow transplantation has not been determined.

Imatinib is indicated for:

- The treatment of adult patients with Kit (CD 117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST).
- The adjuvant treatment of adult patients who are at significant risk of relapse following resection of Kit (CD117)-positive GIST. Patients who have a low or very low risk of recurrence should not receive adjuvant treatment.
- The treatment of adult patients with unresectable dermatofibrosarcoma protuberans (DFSP) and adult patients with recurrent and/or metastatic DFSP who are not eligible for surgery.

In adult and paediatric patients, the effectiveness of imatinib is based on overall haematological and cytogenetic response rates and progression-free survival in CML, on haematological and cytogenetic response rates in Ph+ ALL, MDS/MPD, on haematological response rates in HES/CEL and on objective response rates in adult patients with unresectable and/or metastatic GIST and DFSP and on recurrence-free survival in adjuvant GIST. The experience with imatinib in patients with MDS/MPD associated with PDGFR gene rearrangements is very limited (see section 5.1 of the SmPC). There are no controlled trials demonstrating a clinical benefit or increased survival for these diseases.

The following indications which are covered by orphan designation for Tasigna (nilotinib) were not applied for:

Tasigna
150 mg

- *Treatment of adult patients with newly diagnosed Philadelphia-chromosome-positive chronic myelogenous leukaemia (CML) in the chronic phase.*

200 mg
Treatment of adult patients with:

- *newly diagnosed Philadelphia-chromosome-positive CML in the chronic phase;*
- *chronic phase and accelerated phase Philadelphia-chromosome-positive CML with resistance or intolerance to prior therapy including imatinib.*

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 Glivec 100 mg and 400 mg film-coated tablets which have been registered by

Novartis Europharm Limited in the EEA (EU product number: EMEA/H/C/000406) since 7 November 2001 by the centralised procedure EU/1/01/198/002-006.

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Czech Republic, Germany, Finland, France, Ireland, Lithuania, Latvia, Malta, Romania, Sweden, Slovenia and the United Kingdom.

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

II. QUALITY ASPECTS

II.1 Introduction

Imatinib Koanaa are film-coated immediate release tablets in the strengths of 100 mg and 400 mg imatinib, as 119.5 mg and 478 mg imatinib mesilate respectively.

The 100 mg film-coated tablets are dark yellow to brownish orange coloured, film-coated tablets, round, biconvex with bevelled edges debossed with 'S' and '1' on either side of break line on one side and plain on other side.

The 400 mg film-coated tablets are dark yellow to brownish orange coloured, film-coated tablets, capsule shaped, biconvex with bevelled edges debossed with 'S' and '2' on either side of break line on one side and plain on other side.

Both tablet strengths can be divided into equal doses.

The film-coated tablets are packed in clear PVC/PVDC/Aluminium foil blister packs.

The excipients are:

Tablet core
- Povidone K30
- Magnesium stearate (E572)

Tablet coat
- Hypromellose (E464)
- Macrogol 3350
- Talc (E553)
- Titanium dioxide (E171)
- Iron oxide red (E172)
- Iron oxide yellow (E172)

The two tablet strengths are dose proportional.

II.2 Drug Substance

The active substance is imatinib mesilate, an established substance not described in a Pharmacopoeia. Imatinib mesilate is an off white to pale yellow crystalline powder and it is freely soluble in water, slightly soluble in methanol and 2-propanol, and insoluble in heptane and pentane. It neither has asymmetric carbons, nor centres of chirality. The drug substance exhibits polymorphism. Hence, form α is produced. Imatinib mesilate is not hygroscopic under conditions applied during production and storage.

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 imatinib mesilate (form-α) involves three stages. The drug substance is sufficiently characterised with regard to chemical structure and polymorphic form. The intended polymorphic form α is consistently manufactured, and has also been demonstrated to be stable. The discussion on impurities is appropriate.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the European Pharmacopoeia (Ph.Eur.). In-house methods have adequately been described and validated. Batch analytical data demonstrating compliance with this specification have been provided for three production scaled 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 (12 months) and 40°C/75% RH (6 months). All results comply. These data are sufficient to support the proposed re-test of one year.

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 formulation development is straightforward based on the composition of the reference product. As a fixed composition and manufacturing process is applied, this compact development is appropriate. Both tablet strengths contain a break line. Correct divisibility and ease of breaking, has been demonstrated in line with the Ph.Eur. monograph 'Tablets', and also confirmed during storage. The instruction to administer the tablets by dispersing the tablets in water or apple juice has been supported by stability data and comparison of the disintegration time with the reference product.

A bioequivalence study was carried out with the 400 mg strength. A biowaiver was requested for the 100 mg strength. The biowaiver is acceptable from a chemical pharmaceutical point of view. Similar *in vitro* dissolution profiles were obtained for the 100 mg and 400 mg strengths of the test and reference product in three different buffers (pH 1.2, 4.5 and 6.8). All profiles show >85% of the drug dissolved in 15 minutes.

Manufacturing process
The drug product is prepared by conventional wet granulation process followed by compression. Adequate in-process controls and controls of intermediate products are applied. The process is a standard manufacturing process. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for sufficient small production batches in accordance with the relevant European guidelines.

Control of excipients
For all excipients reference is made to the Ph.Eur, except for the Opadry coating. For the iron oxide of Opadry, compliance with EU Directive on colourants 95/45/EC, replaced by Directive 2008/128/EC and subsequently Commission Regulation (EU) No 231/2012 is confirmed. 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, identity, average weight, dimensions, water content, content isopropyl alcohol, uniformity of dosage units, assay, degradation (purity), alkyl methane mesilate esters, dissolution and microbiological quality. 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 six batches 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 18 months storage at 25°C/60% RH and six months storage at 40°C/75% RH. The only trend observed is a slight decrease in dissolution. It is demonstrated that the tablets are not sensitive for light. Based on these results the proposed shelf-life of two years and storage condition (no specific requirement) 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 Imatinib Koanaa 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 Imatinib Koanaa 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 Glivec 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

Imatinib mesilate 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 a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

Bioequivalence study
The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Imatinib Koanaa 400 mg film-coated tablets (Koanaa Healthcare Limited, UK) is compared with the

pharmacokinetic profile of the reference product Glivec 400 mg film-coated tablets (Novartis Europharm Limited, UK).

The choice of the reference product
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 results of the bioequivalence study with the 400 mg formulation can be extrapolated to the other strength (100 mg), according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6: Both strengths are manufactured by the same process, the two strengths have a dose-proportional composition, and comparable dissolution was demonstrated for the 100 and 400 mg strengths. Finally, linear kinetics has been reported for imatinib.

Design
A monocentric, single-dose, randomised, open-label, two-treatment, two-way crossover bioequivalence study was carried out under fed conditions in 24 healthy male subjects. Each subject received a single dose (400 mg) of one of the two imatinib formulations. The tablet was orally administered with 240 ml water 30 minutes after finishing a high fat, high calorie breakfast. There were two dosing periods, separated by a washout period of ten days.

Blood samples were collected at pre-dose and at 0.5, 1.0, 1.50, 2.0, 2.5, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.33, 5.67, 6, 6.5, 7, 8, 10, 12, 16, 24, 36, 48, and 72 hours after administration of the products.

The design of the study is acceptable. The length of the sampling period was sufficient as well as the sampling frequency to estimate the expected pharmacokinetic parameters. Imatinib is recommended to be taken only in the fed state, therefore, it is acceptable that the bioequivalence study is conducted under fed conditions.

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 did not report to facility in period II; One subject reported an adverse event (vomiting) in period II before dosing, and hence was withdrawn from the study. Two subjects reported an adverse event (vomiting) in period II after dosing, hence withdrawn from the study in period II. Therefore, 19 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=19	**AUC_{0-t}** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	24919 ± 9294	1320.6 ± 477	4.33 (1.5 - 8.0)
Reference	23027 ± 5732	1392.0 ± 346	3.33 (2.0 - 5.3)
***Ratio (90% CI)**	1.04 (0.93 - 1.16)	0.93 (0.81 - 1.07)	--
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 Imatinib Koanaa is considered bioequivalent with Glivec.

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 Imatinib Koanaa.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Myelosuppression • Oedema and fluid retention • Central nervous system (CNS) and gastrointestinal (GI) haemorrhages • Gastrointestinal obstruction, perforation or ulceration • Hepatotoxicity • Skin rashes and severe cutaneous reactions • Hypothyroidism • Hypophosphataemia • Cardiac failure • Acute renal failure • Severe respiratory adverse reactions • Rhabdomyolysis and myopathy • Ovarian haemorrhage and haemorrhagic ovarian cyst • Tumour lysis syndrome • Growth retardation in children • Interaction with strong CYP3A4 inducers • Interaction with drugs eliminated by CYP3A4
Important potential risks	• Second malignancies in survivors • Disseminated intravascular coagulation • Tolerability during pregnancy and pregnancy outcomes • Interaction with drugs eliminated by CYP2C9, CYP2C19 and CYP2D6 • Interaction with acetaminophen/paracetamol • Hypoglycaemia • Suicidality
Missing information	• Paediatric patients: Long term follow up • Paediatric patients below two years of age • Use in elderly patients • Renal impairment • Hepatic impairment

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 Glivec. 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 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 PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Imatinib Koanaa 100 mg and 400 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Glivec 100 mg and 400 mg film-coated tablets. Glivec 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 Imatinib Koanaa with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 21 September 2016.

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/3510/IA/002/G	Replacement or addition of a site where batch control/testing takes place	--	29-10-2017	Approval	--
NL/H/3510/IA/001/	Change within the range of currently approved pack sizes	--	10-8-2017	Non-approval	--
NL/H/3510/IA/003/	Change within the range of currently approved pack sizes	--	15-10-2017	Approval	--