CBG MEB

Public Assessment Report

Scientific discussion

Imatinib Amarox 100 mg and 400 mg film-coated tablets

(imatinib mesilate)

NL/H/3726/001-002/DC

Date: 4 January 2018

This module reflects the scientific discussion for the approval of Imatinib Amarox 100 mg and 400 mg film-coated tablets. The procedure was finalised on 14 June 2017. 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
USNF	

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Imatinib Amarox 100 mg and 400 mg film-coated tablets, from Hetero Europe S.L.

The product is indicated for the treatment of:

- 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 hyper-eosinophilic 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 (CD 117)-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 the products Sprycel (dasatinib) and Tasigna (nilotinib) were not applied for:

Sprycel
Treatment of adult patients with:
- *newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukaemia (CML) in the chronic phase.*
- *chronic, accelerated or blast phase CML with resistance or intolerance to prior therapy including imatinib mesilate.*
- *Ph+ acute lymphoblastic leukaemia (ALL) and lymphoid blast CML with resistance or intolerance to prior therapy.*

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.*

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 centralised procedure EU/1/01/198/002-006.

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

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

II. QUALITY ASPECTS

II.1 Introduction

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

The 100 mg film-coated tablets are brownish orange coloured, round, bevel edged scored with a dimension of approximately 7.1 mm, debossed with H on one side and 19 on the other side, 1 and 9 separated by a score line.

The 400 mg film-coated tablets are brownish orange coloured, capsule shaped, bevel edged scored with a dimension of approximately 15.0 mm in length and 6.5 mm in width, debossed with H on one side and 20 on the other side, 2 and 0 separated by a score line.

The tablets of both strengths can be divided into equal doses along the score line.

The film-coated tablets are packed in Alu/Alu blisters or HDPE containers with polypropylene cap and silica gel desiccant.

The excipients are:

Tablet core:
- Magnesium stearate

Tablet coating:
- Hypromellose (E464)
- Titanium dioxide (E171)
- Yellow iron oxide (E172)
- Red iron oxide (E172)
- Talc (E553b)
- Macrogol (E1521)

The two tablet strengths are dose proportional.

II.2 Drug Substance

The active substance is imatinib mesilate, an established substance described in the European Pharmacopoeia (Ph.Eur.). Imatinib mesilate is a white to pale yellow 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. 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 ASMF holder produces the drug substance in six stages. The drug substance is sufficiently characterized with regard to chemical structure and polymorphic form. The intended polymorphic form α is consistently manufactured, and has also been demonstrated to be stable in drug substance and drug product.

Quality control of drug substance
The drug substance specification of the MAH is identical to the drug substance specification of the ASMF holder with some additional tests for particle size, tapped and bulk density and microbiological purity. The proposed drug substance specification is in accordance with the requirements of the Ph.Eur. monograph. The limits are acceptable, and in line with the specifications of the ASMF-holder. Batch analytical data demonstrating compliance with this specification have been provided.

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) and 40°C/75% RH (6 months). No significant changes were observed in the currently available stability data. Based on the provided stability data, the proposed re-test period of 60 months is acceptable. The drug substance is photostable.

II.3 Medicinal Product

Pharmaceutical development
The products are established pharmaceutical forms and their development is adequately described in accordance with the relevant European guidelines. The development of the product has been described, the choice of excipients is justified and their functions explained. Breakability of the tablets has been demonstrated in accordance with the Ph. Eur. test and criteria. Although the qualitative composition of the generic products differs from that of the reference product, the dissolution is similar, for both the tablet strengths.

A bioequivalence study was carried out with the 400 mg strength. The dissolution profiles obtained of the generic products and reference product were similar at pH 1.0 and 4.5 (>85 % dissolved in 15 minutes). At pH 6.8 there was a minor difference of 10%. No point was raised as bioequivalence was shown *in vivo* (see section IV.2 'Pharmacokinetics').

A biowaiver was requested for the 100 mg strength. This is acceptable considering that both strengths (100 mg and 400 mg) are fully dose proportional and are manufactured using the same manufacturing process. In addition dissolution profiles of both strength across the physiological pH range are similar. The general biowaiver criteria are thereby met and the requested biowaiver for the 100 mg strength can be granted.

Manufacturing process
The description of the manufacturing process is sufficiently detailed. The manufacturing process includes dry blending, compression, and film-coating. The manufacturing process is regarded as a standard process. The holding times at the different stages are laid down, and have been sufficiently justified with stability data.
The process has been sufficiently validated. Process evaluation data were presented for two batches of each strength. All batches complied with the predefined acceptance criteria. Acceptable process validation protocols have been provided for the next production batches after product approval.

Control of excipients
All individual excipients comply with the Ph. Eur. except for the colorants. The colorants Iron oxide yellow (E172) and Iron oxide red (E172) are in accordance with the requirements as included in Commission Regulation (EU) No. 231/2012.

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, ferric oxide identification, average weight, loss on drying, dissolution, uniformity of dosage units, degradation products, assay, and microbial limits. 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 2 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 was provided for two batches of each strength at semi-industrial size stored at 25°C/60% RH (24 months), 40°C/75% RH (6 months) and 30°C/65%RH (12 months). The conditions used in the stability studies are according to the ICH stability guideline. Tablets were stored in the proposed packages. No significant changes were observed. Levels of all other degradation products remained below the reporting threshold at both storage conditions. Photostability of the drug product has been demonstrated. Based on the provided stability data, the proposed shelf life of 24 months without specific storage conditions is approvable. The in-use shelf-life for the HDPE container is 90 days after first opening.

Specific measures for the prevention of the transmission of animal spongiform encephalo-pathies
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 Amarox 100 mg and 400 mg film-coated tablets have 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 Amarox 100 mg and 400 mg are 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

These products are generic formulations of Glivec film-coated tablets which are 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 Imatinib Amarox 400 mg film-coated tablets (Hetero Europe S.L., Spain) is compared with the pharmacokinetic profile of the reference product Glivec 400 mg tablets (Novartis Europharm Limited, from the German market).

The choice of the reference product
The choice of the reference product in the bioequivalence study has been justified, as it has been authorised through a centralised procedure. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver
The MAH provided a justification for the biowaiver of conduction bioequivalence studies with the lower 100 mg tablet strength based on the bioequivalence study for the 400 mg tablet strength. Both strengths are manufactured by the same manufacturing process and the qualitative/quantitative (proportional) composition is the same. Also, comparative dissolution between a 100 mg batch of the proposed product and the 400 mg bio batch was submitted in the four different media. For 0.1 N HCl, purified water and pH 4.5 acetate buffer more than 85% was dissolved in 15 mins for both strengths. For the dissolution medium pH 6.8 phosphate buffer a f2 similarity factor calculation (f2=71.3) demonstrated comparative dissolution.

The biowaiver is acceptable, considering the quantitative proportional compositions and the similar dissolution profiles of the 100 mg and 400 mg strength of the generic product across the physiological pH range.

Design
A balanced, randomised, two-period, two-treatment, two-sequence, single oral dose crossover bioequivalence study was carried out under fed conditions in 36 healthy male subjects, aged 20-44 years. Each subject received a single dose (400 mg) of one of the 2 imatinib mesilate formulations. Subjects fasted overnight and were served a high fat high calorie breakfast. The breakfast was finished within 30 minutes and the dose was orally administered, with 240 ml water, 30 minutes after the start of the breakfast. The total caloric content of the breakfast was 938 kCal, of which 28% carbohydrate, 58% fat and 15% protein. There were 2 dosing periods, separated by a washout period of 8 days.
Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.5, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours post dosing.

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
A total of 36 subjects were dosed in the study, of which 35 subjects completed both periods of the study. One subject dropped out of the study in the 1st period, due to an adverse event (loose stool). A total of 33 subjects were included in the statistical analysis of the AUC and a total of 35 subjects were included in the statistical analysis of the C_{max}. For 2 subjects AUC_{0-t} and $AUC_{0-\infty}$ were not determined as both had 3 consecutive missing samples in the elimination phase. The drop-out rate as well as the exclusion of 2 subjects from the AUC analysis is acceptable.

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

Treatment n=35 [n=33 for AUC]	**AUC_{0-t}** µg/ml/h	**$AUC_{0-\infty}$** µg/ml/h	**C_{max}** µg/ml	**t_{max}** h
Test	35.2 ± 11.9	36.9 ± 12.7	1.9 ± 0.6	3.0 (1.5-6.0)
Reference	34.8 ± 12.3	36.5 ± 13.1	1.9 ± 0.6	3.67 (2.0-8.0)
Ratio (90% CI)	1.02 (0.97-1.07)	1.02 (0.97-1.07)	0.99 (0.94-1.05)	

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
C_{max} Maximum plasma concentration
t_{max} Time until Cmax is reached

**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 Imatinib Amarox 400 mg is considered bioequivalent with Glivec 400 mg.

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 Amarox.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Myelosuppression • Oedema and fluid retention • Gastrointestinal and central nervous system haemorrhage • Gastrointestinal ulceration, perforation and obstruction • Hepatotoxicity • Skin rashes and severe cutaneous reactions • Hypothyroidism • Hypophosphataemia • Cardiac failure • 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 inhibitors • Interaction with strong CYP3A4 inducers • Interaction with drugs eliminated by CYP3A4
Important potential risks	• Second primary malignancy • Disseminated intravascular coagulation • Hypoglycaemia • Suicidality • Tolerability during pregnancy and pregnancy outcomes • Interaction with drugs eliminated by CYP2C9, CYP2C19 and CYP2D6
Missing information	• Paediatric patients: long term follow up • Paediatric patients below 2 years of age • 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

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 the PL of Glivec 100 mg and 400 mg. With regard to layout and design, the MAH indicated that its house style has been successfully user tested in many procedures. The bridging report submitted by the MAH has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Imatinib Amarox 100 mg and 400 mg have a proven chemical-pharmaceutical quality and are generic forms of Glivec 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 Amarox with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 14 June 2017.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE – SUMMARY

Procedure number	Scope	Product Information affected	Date of end of the procedure	Approval/ non approval	Summary/ Justification for refuse