CBG MEB

Public Assessment Report

Scientific discussion

Imatinib Sandoz 100 mg and 400 mg, film-coated tablets

(imatinib mesilate)

NL/H/3319/001-002/DC

Date: 7 July 2016

This module reflects the scientific discussion for the approval of Imatinib Sandoz 100 mg and 400 mg, film-coated tablets. The procedure was finalised on 14 October 2015. 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 Imatinib Sandoz 100 mg and 400 mg, film-coated tablets from Sandoz B.V.

The product is indicated for the treatment of:

- Adult and 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.
- Adult and paediatric patients with Ph+ CML in chronic phase after failure of interferon-alpha therapy, or in accelerated phase or 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.
- Adult patients with unresectable dermatofibrosarcoma protuberans (DFSP) and adult patients with recurrent and/or metastatic DFSP who are not eligible for surgery.

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

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 DFSP. 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 were not applied for:

- *The treatment of adult patients with Kit (CD117) 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.*

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Glivec 100 mg and 400 mg film-coated tablets. Imatinib containing medicinal products 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/1/01/198/001-006. The MAH included a statement of identity declaring that Imatinib Sandoz tablets are qualitatively and quantitatively identical to Glivec tablets.

The concerned member states (CMS) involved in this procedure were Austria, Germany and Malta.

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

II. QUALITY ASPECTS

II.1 Introduction

Imatinib Sandoz is a film-coated immediate release tablet 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 very dark yellow to brownish orange, round, biconvex film-coated tablets with bevelled edges, debossed with “NVR” on one side and “SA” and score between the letters on the other side. Approximate diameter 9.2 mm.

The 400 mg film-coated tablets are very dark yellow to brownish orange, ovaloid, biconvex film-coated tablets with bevelled edges, debossed with “400” on one side and score on the other side and SL on each side of the score. Approximate length 19.2 mm and width 7.7 mm.

Both tablet strengths have a score line, which is suitable to divide the tablets into equal halves.

The drug products are packed in PVC-PE-PVDC/Al blisters (both strengths) or PVC/Al-blisters (only 100 mg).

The excipients are:

Tablet core
- Cellulose microcrystalline
- Crospovidone (type A)
- Hypromellose
- Magnesium stearate
- Silica, colloidal anhydrous

Tablet coat
- Iron oxide, red (E172)
- Iron oxide, yellow (E172)
- Macrogol 4000
- Talc
- Hypromellose

The different tablet strengths are fully dose proportional with regards to their tablet cores.

II.2 Drug Substance

The active substance is imatinib mesilate, an established active substance not described in a Pharmacopoeia. Imatinib mesilate is a white to off-white to brownish or yellowish tinged powder and it is very to freely soluble in water and aqueous solutions at low pH values, it is soluble in polar solvents such as methanol and ethanol but only slightly soluble to insoluble in low polar solvents. It neither has asymmetric carbons, nor centres of chirality. The drug substance exhibits polymorphism. The compound can crystallize in two different crystalline forms (A and B) and is manufactured as form B for the drug product.

Manufacturing process
The manufacturing process is described in five steps. The first step starts with the starting material that is reacted into a compound used later in the synthesis. The second step starts with the two other starting materials, the fourth starting material is introduced in the second step of the reaction. The last step of the synthesis concerns the formation of the imatinib mesilate salt. No class 1 organic solvents are used in the synthesis. The active substance has been adequately characterised and acceptable specifications have been adopted for the starting materials, solvents and reagents.

Quality control of drug substance
The drug substance specification has been established in-house by the MAH. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical

data demonstrating compliance with the drug substance specification have been provided for three full scaled batches.

Stability of drug substance
Stability data on the active substance have been provided for three full scaled batches stored at 25°C/60% RH (60 months), 30°C/65% RH (60 months) and 40°C/75% RH (6 months). No trends or changes were observed in any of the tested parameters at all three storage conditions. The proposed retest period of 60 months with storage condition 'Store below 30°C' 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 choices of the packaging, manufacturing process and the choice of excipients are appropriate. Both tablet strengths have score lines, which are suitable to divide the tablets into equal halves. Compliance with the test for subdivision of tablets as described in the general Ph.Eur. monograph on tablets has been confirmed.

The products are identical to the reference product, with the exception that the 400 mg film-coated tablets obtain a score line which is not present on the authorised 400 mg reference product. It is shown by *in vitro* studies that the score line did not affect the drug product's dissolution properties (>85% in 15 minutes in media covering the physiological pH range) compared to the authorized Glivec 400 mg tablet without a score line.

Manufacturing process
The main steps in the manufacturing process are dry mixing, wet granulation and drying, blending and lubrication, compression and coating. The 100 mg tablets are manufactured at two different manufacturing sites. The 400 mg tablets are only manufactured at one site. The manufacturing process is a standard process and has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full scaled batches per strength and for both manufacturing sites for the 100 mg tablets.

Control of excipients
Except for the film-coating materials, the excipients comply with the Ph.Eur. The individual components of the film-coating materials comply with the Ph.Eur. or relevant regulatory requirements. 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 description, identification, mean mass, dissolution, impurities microbial quality, uniformity of dosage units and assay. 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 the proposed production sites have been presented on at least six full scale batches of both tablet strengths have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided on two full scaled batches of both strengths that were stored at 25°C/60% RH (up to 36 months), 30°C/65% RH or 75% RH (up to 36 months) and 40°C/75% RH (6 months) for batches from one manufacturer. In addition stability data were provided on three full scaled batches of the second manufacturer (producing only 100 mg tablets) that were stored at 30°C/75% RH (36 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 the proposed packages. Except for a slight increase in one impurity, no trends or changes were observed in any of the tested parameters. All parameters remained within the acceptance criteria. Results of a photostability study showed that the drug product is not sensitive to light exposure. The proposed shelf-life of 3 years and storage conditions 'Do not store above 30°C' and 'Store in the original package in order to protect from moisture' can be accepted.

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 Sandoz 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 Sandoz 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 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.

IV.2 Pharmacokinetics

Biowaiver
The MAH of the reference product has submitted an identity statement that the products under review here, Imatinib Sandoz 100 mg and 400 mg, film-coated tablets, and the reference (innovator) product Glivec are identical. Hence Imatinib Sandoz is produced with the same qualitative and quantitative composition, at the same manufacturing site, using the same manufacturing procedure and the same source of active substance as their currently manufactured reference product. The difference between the 400 mg divisible and non-divisible tablets is not expected to have any influence in pharmacokinetic properties, dissolution over the physiological pH range is similar for the divisible and the non-divisible form. Thus, the Imatinib Sandoz 400 mg divisible tablets can be considered the same as the Glivec non-divisible 400 mg tablets.
As the member states have been ensured that Imatinib Sandoz 100 mg and 400 mg film-coated tablets are identical to the reference product Glivec, a biowaiver has been granted.

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 Sandoz.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Myelosuppression • Oedema and fluid retention • GI and CNS haemorrhage • GI ulceration, perforation and obstruction • 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 • Cerebral haemorrhage • Hypophosphataemia • Drug interaction - Strong CYP3A4 inhibitors • Drug interaction - Strong CYP3A4 inducers • Drug interaction - Drugs eliminated by CYP3A4
Important potential risks	• Second Malignancies in Survivors • Disseminated intravascular coagulation • Hypoglycaemia • Suicidality • Tolerability during Pregnancy and Pregnancy outcomes • Drug interaction - Drugs eliminated by CYP2C9, CYP2C19 and CYP2D6 • Drug interaction - Acetaminophen/ paracetamol
Missing information	• Paediatric population • Paediatric patients below 2 years of age • Renal impairment • Hepatic impairment • Elderly patients

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 film-coated tablets. No new clinical studies were conducted. The MAH of the reference product demonstrated through an identity statement that the Imatinib Sandoz is identical to the reference product. Therefore bioequivalence testing is not required. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The MAH did not perform a user consultation for Imatinib Sandoz 100 mg and 400 mg, film-coated tablets as the package insert belongs to the same medicinal class, and the key messages on it, are identical to reference product Glivec. The last user consultation for Glivec was performed in 2010 (variation NL/H/II/59). The Sandoz layout and design was successfully tested previously.
Patients will assess the package leaflet of the Imatinib Sandoz package equally well, while also being able to comprehend and subsequently act upon it. The member states agree that additional user testing is not required.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Imatinib Sandoz 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.

The MAH did not submit a bioequivalence study, but provided sufficient information to demonstrate that the product has the same quantitative and qualitative composition as Glivec and is produced in the same manufacturing site.

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 Sandoz with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 14 October 2015.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE – SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Replacement or addition of a site where batch control/testing takes place. Minor change in the manufacturing process.	NL/H/3319/IB/001/G	IB	30-5-2016	29-6-2016	Approval	No
Update SmPC and PUIL in order to include PRAC recommendations on signals Bcr-abl tyrosine kinase inhibitors. PRAC recommendations on signals.	NL/H/3319/1-2/IA/002	IA	9-5-2016	8-6-2016	Approval	No
MAH proposes to add adult CML indications in line with reference product Glivec	NL/H/3319/IB/003	IB	3-6-2016	1-7-2016	Approval	No