COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Bimatix 100 mg and 400 mg, film-coated tablets (imatinib mesylate)

NL/H/5908/001-002/DC

Date: 24 February 2025

This module reflects the scientific discussion for the approval of Bimatix 100 mg and 400 mg, film-coated tablets. The procedure was finalised on 13 November 2024. 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
EMA	European Medicines Agency
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
RMS	Reference Member State
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 Bimatix 100 mg and 400 mg, film-coated tablets, from Stada Arzneimittel AG.

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.

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

The product 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 re-arrangements is very limited (see section 5.1 of the SmPC). Except in newly diagnosed chronic phase CML, there are no controlled trials demonstrating a clinical benefit or increased survival for these diseases.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Glivec 100 and 400 mg film-coated tablets which has been registered in the EEA via the centralised procedure EU/1/01/198 (EMEA/H/C/406) by Novartis Europharm Limited Ireland, since 7 November 2001.

The concerned member states (CMS) involved in this procedure were Denmark, Finland, Iceland, Norway and Sweden.

Similarity assessment

According to Article 8(1) of Regulation (EC) No 141/2000, no marketing authorisation can be granted for a product similar to an orphan medicinal product for a period of ten years, when this concerns a similar medicinal product with the same therapeutic indication. The MAH has provided a similarity assessment between Bimatix, film-coated tablets and the current orphan products authorised in the EU. These orphan products and their respective indications are:

- Indicated for the treatment of chronic myeloid leukaemia (Ph+ CML-CP):
    - SCEMBLIX (asciminib hydrochloride), Novartis Europharm Limited Ireland, EU/1/22/1670
- Indicated for the treatment of acute lymphoblastic leukaemia (ALL):
    - Tecartus (brexucabtagene autoleucel), Kite Pharma EU B.V., EU/1/20/1492
    - Kymriah (tisagenlecleucel), Novartis Europharm Limited, EU/1/18/1297
    - BESPONSA (inotuzumab ozogamicin), Pfizer Europe MA EEIG, EU/1/17/1200
    - BLINCYTO (blinatumomab), Amgen Europe B.V., EU/1/15/1047
- Indicated for the treatment of myelodysplastic syndromes (MDS):
    - Reblozyl (luspatercept), Bristol Myers Squibb Pharma EEIG, EU/1/20/1452
- Indicated for the treatment gastrointestinal stromal tumours (GIST):
    - QINLOCK (ripretinib), QINLOCK (ripretinib), EU/1/21/1569
    - AYVAKYT (avapritinib), Blueprint Medicines (Netherland s) B.V., EU/1/20/1473

The assessment included the comparison of the therapeutic indication, active substance, mechanism of action and principal (molecular) structure. After consideration of the MAH arguments, Bimatix is not considered similar to the orphan products with regard to the therapeutic indication (as defined in Article 3 of Commission Regulation (EC) No. 847/2000). Therefore, the existence of any market exclusivity for Scemblix, Tecartus, Kymriah, BESPONSA, BLINCYTO, Reblozyl, QINLOCK, AYVAKTY in the treatment of CML, Ph+ ALL, MDS/MPD, or GIST does not prevent the granting of the marketing authorisation for Bimatix.

II. QUALITY ASPECTS

II.1 Introduction

Bimatix are film-coated tablets containing 100 mg or 400 mg imatinib (as mesylate) as active substance. The tablets of the different strengths can be distinguished by their shape and size and are as follows:

Bimatix 100 mg is a dark yellow to brownish yellow, biconvex, round, film-coated tablet, with a breaking notch on one side and an average thickness of approx. 3.5 mm and a diameter of approx. 9.2 mm. Each film-coated tablet contains imatinib mesylate equivalent to 100 mg imatinib.

Bimatix 400 mg is a dark yellow to brownish yellow, biconvex, oval, film-coated tablet, with a breaking notch on one side and an average thickness of approx. 7.3 mm, length of approx. 18.4 mm and width of approx. 7.3 mm. Each film-coated tablet contains imatinib mesylate equivalent to 400 mg imatinib.

The excipients for strength 100 mg and 400 mg are:

Tablet core - microcrystalline cellulose, hypromellose (E464), crospovidone (Type A), silica colloidal anhydrous and magnesium stearate (E572).
Tablet coat - hypromellose (E464), iron oxide yellow (E172), iron oxide red (E172) and talc (E553b).

The two tablet strengths are fully dose proportional. The tablets can be divided into equal doses.

The film-coated tablets are packed in polyvinyl chloride/polypropylene/polyvinylidene dichloride/aluminium (PVC/PE/PVdC-Al) blisters.

II.2 Drug Substance

The active substance is imatinib mesilate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white, yellowish crystalline powder and is freely soluble in water. The drug substance shows polymorphism, for this product the polymorphic β form is consistently produced by the manufacturer. The stability of this polymorphic form during storage of the drug substance has been demonstrated.

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 manufacturing process consists of several steps for synthesis and a final purification step. The active substance and materials used in the synthesis have been adequately characterised and adequate specifications are adopted to control their quality. Characterisation of the (potential) impurities is adequately performed, submitted studies show that all potentially toxic impurities are sufficiently controlled. The active substance has been adequately characterised and the manufacturing process is described in sufficient detail.

Quality control of drug substance

The active substance specification has been justified and is considered adequate to control the quality. The specification is according to the ASMF and meets the requirements of the monograph in the Ph.Eur. with additional in-house requirements for particle size distribution. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

Stability data on the active substance have been provided for three 3 commercial scale batches in accordance with applicable European guidelines. Based on the data submitted, a retest period of 24 months could be granted, when stored under the stated conditions.

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 chosen β polymorphic form of the drug substance and the chosen excipients are the same as in the reference product. The main development studies were the characterisation of the reference products, optimisation of the formulation and development of the dissolution method. A bioequivalence (BE) study has been performed with the 400 mg product. The test batch used in the BE study was manufactured according to the finalised formulation and manufacturing process at a representative scale. For the 100 mg strength a biowaiver was granted, see details in section IV.2. In support of the BE and biowaiver, comparative *in vitro* dissolution testing at pH 1.2, pH 4.5 and pH 6.8 has been adequately performed. Information on aqueous solubility over the physiological pH range have been provided as part of the dissolution method development. Based on these study results, where the highest strength of 400 mg is not completely soluble in 250 mL pH 6.8 medium, the drug substance is considered BCS low soluble. The developed routine dissolution testing method is acceptable, the discriminatory power of the method has been sufficiently demonstrated. The tablets have a break-mark and can be divided into equal doses according to section 3 of the SmPC, which is in line with the 100 mg and 400 mg reference products. Compliance with the Ph.Eur. test for subdivision of tablets was confirmed as part of the development. Bulk stability studies were performed, the proposed bulk holding time is

considered justified. The choice of the packaging and manufacturing process are justified. Overall, the pharmaceutical development of the product has been adequately performed.

Manufacturing process

The main steps of the manufacturing process are dispensing, wet granulation premix, wet granulation, drying, blending, compression, film-coating and packaging. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three pilot scaled batches per strength. The product is manufactured using conventional manufacturing techniques. Process validation for full scaled batches will be performed post authorisation. The proposed holding time process intermediates are acceptable.

Control of excipients

The excipients comply with Ph.Eur. requirements where available, with acceptance limits for additional functionality-related characteristics where relevant. The iron oxide colourants comply with Regulation 231/2012 and the film-coating premix with in-house requirements. 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 appearance, identity, assay, mass variation (uniformity of dosage units), dissolution, related substances, and microbiological quality. The release and shelf-life requirements are identical. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamine risk evaluation has been provided. Batch data on three batches of each strength have been submitted, consistently demonstrating levels of nitrosamines well below the acceptable limit. This justifies the absence of any further testing for nitrosamine impurity in the drug substance and drug product. An elemental impurities risk assessment was submitted and found acceptable. The estimations for worst-case total elemental impurity contribution from the excipients are well below 30% of the ICH Q3D oral PDEs.

The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three pilot scaled batches per strength, demonstrating compliance with the release specification.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from the proposed production site have been provided for three pilot scaled batches per strength, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product have been provided for three production scaled batches of each strength stored at 25°C/ 60% RH (24 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 PVC/PE/PVDC-Al blisters. Except for a slight increase in impurities at accelerated conditions, no clear trends or changes were observed. All results were in compliance with the shelf-life specification. The ongoing stability studies will be continued according to the stability

protocol. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. On basis of the data submitted, a shelf life was granted of 3 years. No specific storage conditions needed to be included in the SmPC or on the label.

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 Bimatix 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 Bimatix 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 in accordance with the ERA Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 corr 2) as the application was submitted before 1 September 2024.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Glivec which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was 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 mesylate is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. 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 Imatinib 400 mg film-coated tablets (Stada Arzneimittel AG, Germany) was compared with the pharmacokinetic profile of the reference product Glivec 400 mg film-coated tablets (Novartis Europharm Limited, Ireland). For the 100 mg strength, a biowaver was requested.

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

Biowaiver

The following general requirements must be met where a waiver for additional strength is claimed, according to the EMA Bioequivalence guideline CPMP/EWP/QWP/1401/98 Rev. 1/Corr **:

a. the pharmaceutical products are manufactured by the same manufacturing process,
b. the qualitative composition of the different strengths is the same,
c. the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule),
d. appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

The dissolution tests at pH 1.2, 4.5 and 6.8 show for the test and reference product that more than 85% of the active is released within 15 minutes. Therefore, the profiles can be considered as similar. As all conditions for the biowaiver criteria are met, a biowaiver for the lowest 100 mg strength has been granted.

Bioequivalence

Design

A single-center, open-label, bioanalytical laboratory- blinded, randomised, single-dose, two-treatment, two-period, two-sequence, crossover bioequivalence study was carried out under fed conditions in 30 healthy male subjects, aged 21-62 years. Each subject received a single dose (400 mg) of one of the two imatinib formulations. The tablet was orally administered with 240 mL water. After an overnight fasting period of at least 10 hours and 30 minutes before study drug administration, subjects received a standardised high-fat, high-calorie meal

of 1011 kilocalories. Fluid intake other than water was controlled for each confinement period and for all subjects. Except for water for the drug intake, water consumption was restricted from 1 hour pre-dose to 1 hour after the drug administration. Food was controlled and standardised for each confinement period and for all subjects. There were two dosing periods, separated by a washout period of 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, 7, 9, 12, 16, 24, 36, 48, and 72 hours after administration of the products.

The design of the study is acceptable. According to the SmPC, the product should be administered orally with a meal and a large glass of water to minimise the risk of gastrointestinal irritations. From the literature it is known that the absorption of imatinib is slightly delayed after a high-fat meal. However, food has no relevant impact on the rate or extent of bioavailability. The bioequivalence study under fed conditions is in accordance with the bioequivalence of the generic and reference product, which is demonstrated according to the relevant guidelines from the EMA 'Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) (EMA 2010)' and 'Imatinib hard capsules 50 and 100 mg, film-coated tablets 100 and 400 mg product-specific bioequivalence guidance (EMA/CHMP/315242/2014) (EMA 2015).

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 28 of the 30 subjects completed the study and were eligible for pharmacokinetic analysis. Two subjects were discontinued from the study at check-in of period 2 due to reasons not related to the study treatment (positive COVID-19 result).

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of imatinib, 400 mg under fed conditions.

Treatment N=28	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	30082	31445	1768	3.50 (1.00-6.00)
Reference	29418	30694	1654	4.50 (1.50-7.12)
***Ratio (90% CI)**	102.74 (98.04-107.67)	---	106.34 (99.93-113.16)	---

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity $AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to the last measurable plasma concentration / to t = 72 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**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, Bimatix 400 mg is considered bioequivalent with Glivec 400 mg. The results of the bioequivalence study with the 400 mg formulation can be extrapolated to lower 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.

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 Bimatix 100 mg and 400 mg. At the time of approval, the most recent version of the RMP was version 0.3 signed 20-09-2024.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	• Second primary malignancy • Tolerability during pregnancy and pregnancy outcomes
Missing information	• Paediatric patients below 2 years of age

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. 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. A user consultation with target patient groups on the package leaflet (PL) has been performed based on a bridging report referring to Glivec 100 and 400 mg film-coated tablets (EU/1/01/198/ EMEA/H/C/406) for content and to Pirfenidone 267 mg film-coated tablets (DE/H/7079-7081/1-3/DC) for 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

Bimatix 100 mg and 400 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Glivec 100 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 Bimatix 100 mg and 400 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 13 November 2024.

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.