COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

# Public Assessment Report

# Scientific discussion

# Imatinib Stada 600 mg film-coated tablets (imatinib mesylate)

# NL/H/4926/001/DC

# Date: 6 September 2021

**This module reflects the scientific discussion for the approval of Imatinib Stada 600 mg film-coated tablets. The procedure was finalised at 4 May 2021. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.**

# List of abbreviations

| | |
|---|---|
| ALL | Acute lymphoblastic leukaemia |
| ASMF | Active Substance Master File |
| CEL | Chronic eosinophilic leukaemia |
| 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 |
| CML | Chronic myeloid leukaemia |
| 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 |
| GIST | Gastrointestinal stromal tumours |
| HES | Hypereosinophilic syndrome |
| ICH | International Conference of Harmonisation |
| MAH | Marketing Authorisation Holder |
| MDS/MDP | Myelodysplastic/myeloproliferative diseases |
| PDGFR | Platelet-derived growth factor receptor |
| Ph+ | Philadelphia chromosome positive |
| 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 Stada 600 mg film-coated tablets, from Stada Arzneimittel AG.

Imatinib Stada 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 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 Stada 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. 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 indications and posology is given in the SmPC.

This decentralised procedure concerns a hybrid application claiming essential similarity with the reference products Glivec 100 and 400 mg film-coated tablets which have been registered in the EEA by Novartis Europharm Limited since 11 November 2003 (EU/1/01/198).

The concerned member states (CMS) involved in the current decentralised procedure were Denmark, Finland, Portugal and Sweden.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, a hybrid application, since the strength of the drug product differs from the strength of the innovator products.

Similarity
The applicant has submitted a Module 1.7.1. (similarity), comparing Imatinib Stada with the authorized orphan medicinal products Iclusig, Blincyto, Besponsa, Xaluprine, Kymriah and Ayvakyt. Imatinib is not considered similar to Iclusig, Blincyto, Besponsa, Xaluprine, Kymriah and Ayvakyt, and therefore, the existence of any market exclusivity for any of these products will not prevent the granting of the marketing authorisation of Imatinib Stada.

# II. QUALITY ASPECTS

## II.1 Introduction

Imatinib Stada are film-coated tablets that are white to off-white, capsule shaped, biconvex and debossed with an 'H' on one side and 'I1' on the other side. The 'I' and '1' are separated by a score line. The tablet can be divided into two equal doses. The film-coated tablet contains as active substance imatinib mesylate equivalent to 600 mg imatinib. The film-coated tablets are packed in aluminium/aluminium blisters.

The excipients are:
*Tablet core* - magnesium stearate.

*Tablet coating* - hypromellose (E464), titanium dioxide (E171), macrogol (E1521), talc (E553b).

## II.2 Drug Substance

The active substance is imatinib mesylate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Imatinib mesylate is an off-white to brownish yellow powder, is freely soluble in water, slightly soluble in ethanol and practically insoluble in methylene chloride. Imatinib mesylate exhibits polymorphism; the alpha crystalline form is the actual polymorphic form used in the entire product development.

The CEP procedure is used for imatinib mesylate. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

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 Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for six batches.

Stability of drug substance

Stability data on the active substance have been provided for three batches in accordance with applicable European guidelines demonstrating the stability of the active substance at long term conditions for sixty months and at accelerated conditions for six months. Based on the data submitted, a retest period could be granted of sixty months under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

## II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with relevant European guidelines. The development of the product has been described, the choice of excipients is justified and their functions explained. The development of Imatinib Stada is fully based on the initial development of the reference products. To overcome the European patent ‘EP 1 501 485 B1’, the product formulation was designed to contain an acceptable percentage of the active substance, and the alpha crystal form was selected.

The objective of the formulation development was to develop a new dosage strength for Imatinib Stada, with a dose that is proportional to the formulation of the reference products. In view of that, information on physiochemical characteristics of Glivec 100 mg and 400 mg film-coated tablets has been submitted by the MAH. Furthermore, several formulation optimisation studies were conducted to select amongst others the appropriate amount of magnesium stearate, the coating system, the coating/solvent ratio and the film-coating build-up. Also, studies were performed to compare the impurity profile of the drug product with

that of the innovator products, which revealed comparable levels. Uniformity of dose of halved tablets was demonstrated for two commercial scale batches.

A bioequivalence study was carried out to compare Imatinib Stada with the combination of a 400 mg tablet and two 100 mg tablets of the reference products. The bioequivalence study will be discussed in section IV. In addition to the bioequivalence study, dissolution studies were performed to compare dissolution profiles of the bio test batch and reference batches. The comparative dissolution profiles showed that the profiles of the proposed drug product were not comparable to those of the reference products. However, *in vivo* comparability of the test and reference products was shown in the bioequivalence study performed.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for two batches in accordance with the relevant European guidelines. All batches complied with the predefined acceptance criteria. The manufacturing process includes drying, blending, compressing, and film-coating. The manufacturing process is regarded as a standard process. The description of the manufacturing process is sufficiently detailed. The holding times at the different stages are laid down, and have been sufficiently justified with stability data.

Control of excipients

An in-house specification is applied for the film-coating. For all excipients and components of the film-coating reference is made to the Ph Eur. No novel excipients are used. The specifications are acceptable and the control of excipients is appropriate.

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, titanium dioxide identification, average weight, water content, uniformity of dose of halved tablets, dissolution, uniformity of dosage units, degradation products, assay, microbial limits, and residual coating solvents. The release and shelf life acceptance criteria are equal for all parameters except for water content. 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 commercial scale batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data of the drug product have been provided for two commercial scale batches stored at 25°C/60%RH (36 months), 40°C/75%RH (six 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 blister packaging. Trends observed were a slight decrease in water content and an increase in one degradation impurity. At accelerated storage conditions (40°C/75%RH), the degradation impurity was found to be out of specification after six months. An out of specification for this impurity was also observed in the photostability study. Based

on the provided 36 months long term stability and 12 months intermediate stability data a shelf life of 24 months can be granted with storage condition: Store below 30°C. Store in the original package in order to protect from light.

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 Stada 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 Stada is intended as a substitute for similar imatinib containing products, 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 hybrid formulation of Glivec administered as 1 x 400 mg + 2 x 100 mg 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 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 on the clinical pharmacology, efficacy and safety is adequate and 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 hybrid application, the MAH has submitted a bioequivalence study to compare the bioavailability of Imatinib Stada with the reference products, which is discussed below.

## IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Imatinib Stada 600 mg film-coated tablets (Stada Arzneimittel AG, Germany) is compared with the pharmacokinetic profile of the reference product Glivec 100 and 400 mg film-coated tablets (Novartis Europharm Limited, Ireland). The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of the reference products. The formula and preparation of the bioequivalence batch are identical to the formula proposed for marketing.

Bioequivalence studies

*Design*

A single-dose, randomised, two-period, two-treatment, two-way crossover bioequivalence study was carried out under fed conditions in 36 healthy male subjects, aged 18 - 45 years. Each subject received a single dose (600 mg; 1 x 600 mg test tablet formulation or 1 x 400 mg Glivec + 2 x 100 mg Glivec tablet reference formulation) of the test and reference imatinib formulations. The tablets were orally administered within 30 minutes after the start of intake of a high fat high caloric breakfast (energy content: 931 kcals; 37.12 g proteins, 58.55 g fat, 64 g carbohydrates) with 240 ml water. According to the SmPC, the prescribed dose should be administered orally with a meal and a large glass of water to minimise the risk of gastrointestinal irritations. As such, the fed condition applied in the study is considered adequate. There were two dosing periods, separated by a washout period of 18 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 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*

Two subjects withdrew from the study due to personal reasons. Three subjects were withdrawn due to emesis after tablet administration. 31 subjects were eligible for pharmacokinetic analysis.

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

| Treatment N= 31 | $AUC_{0-t}$ (ng.h/ml) | $AUC_{0-\infty}$ (ng.h/ml) | $C_{max}$ (ng/ml) | $t_{max}$ (h) | $t_{1/2}$ (h) |
|---|---|---|---|---|---|
| **Test** | 39.6 ± 10.0 | 41.1 ± 10.5 | 2.33 ± 0.53 | 2.5 (1.0 – 6.0) | 15.2 ± 2.3 |
| **Reference** | 38.7 ± 9.8 | 40.1 ± 10.3 | 2.25 ± 0.67 | 3.0 (1.0 – 5.5) | 15.2 ± 2.3 |
| ***Ratio (90% CI)** | 1.02 (0.96 – 1.09) | -- | 1.05 (0.97 – 1.14) | -- | -- |
| **CV (%)** | 15.7 | -- | 19.5 | -- | -- |

| | |
|---|---|
| **$AUC_{0-\infty}$** | 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 |
| **$t_{1/2}$** | half-life |
| **CV** | coefficient of variation |

**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 Stada is considered bioequivalent with Glivec administered as 1 x 400 mg + 2 x 100 mg film-coated tablets.

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 Stada.

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

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|---|---|
| Important identified risks | None |
| Important potential risks | • Second primary malignancy<br>• Tolerability during pregnancy and pregnancy outcomes |
| Missing information | • Paediatric patients: long term follow up<br>• 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 products Glivec 100 mg and 400 mg film-coated tablets. The overview on the clinical pharmacology, efficacy and safety is adequate. No new clinical studies were conducted, which is acceptable for this hybrid procedure. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference products. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the combination of the reference products.

## 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 Glivec film-coated tablets (EU/1/01/198) for the content of the text, and to Imatinib Cell Pharm 400 mg, capsules hard (DE/H/3984/002-03/DC), for the layout of the PL. 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

Imatinib Stada 600 mg film-coated tablets has a proven chemical-pharmaceutical quality and is a hybrid form of Glivec administered as 1 x 400 mg + 2 x 100 mg film-coated tablets. Glivec are well-known medicinal products with an established favourable efficacy and safety profile. Bioequivalence has been shown to be in compliance with the requirements of European guidance documents. Both the non-clinical overview on pharmacology, pharmacokinetics and toxicology, as well as the clinical overview on the clinical pharmacology, efficacy and safety, are adequate. These scientific overviews justify that no new (non)-clinical studies were considered necessary.

The Board followed the advice from 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 Stada with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 4 May 2021.

## 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/4926/001/IA/004 | Type IA: B.II.e.5.a.1<br><br>Change within the range of the currently approved pack sizes. | PL, SmPC, Lab | | | |
| NL/H/4926/001/IB/003 | Type IB: B.III.1.a.2<br><br>Updated certificate from an already approved manufacturer. | no | 02-9-2021 | Approved | |
| NL/H/4926/1/IA/002 | Type IA: A.6<br><br>Change in ATC Code/ ATC Vet Code. | PL, SmPC | 28-7-2021 | Approved | |
| NL/H/4926/001/IB/001 | Type IB: C.I.2.a<br><br>Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/biosimilar medicinal products following assessment of the same change for the reference product - Implementation of change(s) for which no new additional data is required to be submitted by the MAH. | PL, SmPC | 11-8-2021 | Approved | |
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