COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Imatinib Vocate 600 mg, film-coated tablets (imatinib mesilate)

NL/H/5508/001/MR

Date: 29 November 2024

This module reflects the scientific discussion for the approval of Imatinib Vocate 600 mg, film-coated tablets. The procedure was finalised on 27 June 2023. 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
DFSP	Dermatofibrosarcoma Protuberans
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
GC	Gas Chromatography
GIST	Gastrointestinal Stromal Tumours
HES	Hypereosinophilic Syndrome
HPLC	High-Performance Liquid Chromatography
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MDS/MPD	Myelodysplastic/Myeloproliferative Diseases
PDGFR	Platelet-Derived Growth Factor Receptor
Ph+	Philadelphia chromosome (bcr-abl) positive
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 Imatinib Vocate 600 mg, film-coated tablets, from Vocate Pharmaceuticals SA.

The product is indicated for:

- 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 the product 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.

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(3) of Directive 2001/83/EC, which concerns a hybrid application.

In this mutual recognition procedure, essential similarity is proven between the new product and the innovator product Glivec 100 mg and 400 mg film-coated tablets, which have been registered in the EEA via a centralised procedure (EU/1/01/198) since 2001. At the moment, the reference product Glivec (Imatinib) only concern film coated tablets in the strengths of 100 mg and 400 mg. However, the product information leaflet of Glivec (Imatinib) indicates a

dose of 600 mg for adults with Ph+ CML accelerated phase or Blast phase once daily and in adult patients with relapsed or refractory Ph+ ALL. With the offered strengths from the innovator, 600 mg has to be given by taking 1 x 400 mg and 2 x 100 mg, which is inconvenient for patients and can reduce compliance. The 600 mg has been developed to allow breaking in two half tablets, containing 300 mg imatinib. Given the new strength, the application concerns a hybrid application under article 10(3) of Directive 2001/83/EC.

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

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. A similarity assessment has been performed between Imatinib Vocate and Iclusig, Blincyto, Kymriah, Besponsa, Reblozyl, Qinlock and Ayvakyt. Iclusig obtained orphan market exclusivity on 1/7/2013, based on designation EU/3/09/715 and EU/3/09/716. Blincyto obtained orphan market exclusivity on 23/11/2015, based on designation EU/3/09/650. Kymriah obtained orphan market exclusivity on 27/8/2018, based on designation EU/3/14/1266. Besponsa obtained orphan market exclusivity on 3/7/2017, based on designation EU/3/13/1127. Reblozyl obtained orphan market exclusivity on 25/06/2020, based on designation EU/3/14/1331. Qinlock obtained market exclusivity on 24/11/2021, based on designation EU/3/17/1936. Ayvakyt obtained orphan market exclusivity on 24/9/2020, based on designation EU/3/17/1889. The similarity assessment report concluded the products were not similar and that according to the application form there are more products that have been designated as orphan medicinal products, but have not yet been granted a marketing authorisation in the EU. The applicant should monitor these products during the entire procedure to check if a marketing authorisation has been granted. In case a marketing authorisation is granted, the applicant should update the report on similarity (Module 1.7.1) and, if applicable, the data to support derogation from orphan market exclusivity (Module 1.7.2).

II. QUALITY ASPECTS

II.1 Introduction

Imatinib Vocate 600 mg is a white to off-white, capsule shaped, biconvex film-coated tablet. It is debossed with H on one side and I1 on the other side, I and 1 are separated by a score line. The tablet can be divided into two equal doses.

Each tablet contains as active substance 600 mg of imatinib, as 600 mg of imatinib mesilate.

The excipients are:
Tablet core – magnesium stearate.
Tablet coating – hypromellose (E464), titanium dioxide (E171), macrogol (E1521) and talc (E553b).

The film-coated tablet is packed in aluminium/aluminium 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 an off-white to brownish yellow coloured powder. It is freely soluble in water and slightly soluble in ethanol. It is practically insoluble in methyl chloride. The active substance exhibits pH dependent solubility. Solubility decreases with increasing pH above pH 5.5. The active substance has no asymmetric carbons. It exhibits polymorphism. One form is used. It contains no chiral centres and does not exhibit isomerism.

The CEP procedure is used for the active substance. 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. Two CEPs were submitted by the MAH.

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. Additional tests for identification by HPLC (high-performance liquid chromatography) (retention (assay HPLC method), identification of mesilate by precipitation reaction, X-ray diffractogram on solid form, heavy metals mesilate content by potentiometry, and for residual solvents by gas chromatography (GC) were performed. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

CEP 1 does not state a retest period only packaging. However, following stability data has been provided by the applicant:

Stability data on the active substance have been provided for three production scale batches stored at 25°C/60% RH (48 months) and 40°C/75% RH (six months). The stability results comply with the former drug substance specifications according to in-house specifications. Compliance with the new drug substance specifications (according Ph Eur.) will be tested at the 60 month time point. Results of compliance with the Ph Eur. are therefore not yet available, but the specified impurities of the Ph Eur. all concern synthesis impurities and not degradation impurities. In view of that, the 48 months results obtained with the old

specification are also predictive for stability of the active substance. As 12 months extrapolation is allowed, the proposed re-test of 60 months is acceptable.

The re-test period of the active substance of 48 is covered by CEP 2.

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 development of the 600 mg tablets is fully based on the initial development of the reference products of 100 mg and 400 mg tablets strengths. In view of that, information is also included on the development of the 100 mg and the 400 mg tablet strength. The choice of excipients is justified and their functions explained. The qualitative composition of the hybrid product differs from that of the reference product. The dissolution is, however, comparable.
The development specific for the 600 mg strength comprised choice of punch used for the compression, friability, and breakability.
A bioequivalence (BE) study was carried out comparing the dose proportional 400 mg tablet strength with the 400 mg reference product (Glivec 400 mg film-coated tablet) taken from the German market. A biowaiver is proposed for the 600 mg tablet. The same BE study has been used for the approval of the 100 mg and 400 mg tablet strengths. A comparison of the dissolution profiles of the 400 mg biobatch used in the BE study and a 600 mg commercial scale batch (batch IMB115602 – batch size 30,000 tablets) in purified water and in aqueous media 0.1 N HCl, acetate buffer pH 4.5 and phosphate buffer pH 6.8 has been provided. The f2 calculations demonstrate that the dissolution profiles in media 0.1N HCl, acetate buffer pH 4.5 and phosphate buffer pH 6.8 support the biowaiver.
Uniformity of dose of halved tablets was demonstrated for two commercial scale batches.

Manufacturing process

The manufacturing process includes dry blending, compression, and film-coating. The manufacturing process is regarded as a standard process. It has been validated according to relevant European guidelines. Process validation data on the product have been presented for two industrial scaled batches in accordance with the relevant European guidelines.

Control of excipients

All individual excipients comply with the Ph. Eur. 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, 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. 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 batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for two batches stored at 25°C/ 60% RH (18 months) and 40°C/75% RH (6 months) and 30°C/65%RH (12 months). The stability was tested in accordance with applicable ICH stability guidelines. Photostability study determined that the drug product is sensitive to light. On basis of the data submitted, a shelf life was granted of 24 months. The labelled storage conditions are "Do not store above 30°C. Store in the original packaging 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 Vocate 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 Vocate is intended for hybrid substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a hybrid 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 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 member states agreed that no further clinical studies are required, besides the one leading (600 mg) and one supporting bioequivalence study (400 mg), which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study for strength 600 mg in which the pharmacokinetic profile of test product Imatinib Vocate 600 mg, film-coated tablets (Vocate Pharmaceuticals SA, Greece) was compared with the pharmacokinetic profile of the reference product Glivec 400 mg and 2x 100 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 study results and composition. From these dissolution studies it was concluded that Glivec (both the 100 mg and the 400 mg strength) shows more than 85% drug release at 15 min time interval in all dissolution media across the physiological pH range (0.1N HCl, 4.5 pH acetate buffer and 6.8 pH phosphate buffer). 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:

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 MAH provided a justification for the biowaiver based on the bioequivalence study for the 400 mg tablet strength. This study was used for the original registration of Imatinib Hetero 100 mg and 400 mg tablets (NL/H/2987/01). The MAH performed a bioequivalence study with the new 600 mg tablet in order to demonstrate that the biowaiver is also clinical acceptable for the 600 mg strength.

Bioequivalence study

Design

A single-dose, block-randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 36 healthy male subjects, aged 18-45 years. Each subject received a single dose of one of the two imatinib mesilate

formulations. Imatinib Vocate was administered as one tablet of 600 mg, while Glivec was administered as one tablet of 400 mg and two of 100 mg. The tablets were orally administered with 240 mL water after an 8 hour overnight fast, and 30 minutes after being fed a standardised high-fat high-calorie breakfast. There were two dosing periods, separated by a washout period of 8 days.

Blood samples were collected pre-dose and at hours 0,0.5, 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 after administration of the products.

The design of the study is acceptable. 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
36 subjects enrolled in the study. Two subjects dropped out after period I due to adverse events (emesis). Two subjects dropped out prior to period II, one due to personal reasons and the other for failing to present for analysis between periods. One final subject dropped out after period II due to adverse events (emesis). 31 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of imatinib mesilate, 600 mg 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)**
Test	39564.84	41056.54	2333.17	2.5 (1.0 – 6.0)
Reference	38655.52	40125.98	2249.83	3.0 (1.0 – 5.5)
***Ratio (90% CI)**	1.02 (0.96 – 1.09)	-	1.05 (0.97 – 1.14)	-

$AUC_{0-\infty}$	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 the last measurable plasma concentration
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 Imatinib Vocate 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 Vocate.

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: Long term follow up • 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. 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 hybrid 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 language used for the purpose of user testing the PL was English.

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a multiple bridging report making reference to Glivec 400 mg film-coated

tablets, EU/1/01/198. The bridging report submitted by the MAH has been found acceptable; bridging is justified.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Imatinib Vocate 600 mg film-coated tablet has a proven chemical-pharmaceutical quality and is a hybrid form 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 Vocate with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finalised with a positive outcome on 27 June 2023.

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/5508/001 /R/001	Renewal	No	17-11-2023	Approved	N/A