CBG MEB

Public Assessment Report

Scientific discussion

Imatinib Aenorasis 100 mg and 400 mg film-coated tablets

(imatinib mesilate)

NL/H/3470/001-002/DC

Date: 1 June 2016

This module reflects the scientific discussion for the approval Imatinib Aenorasis 100 mg and 400 mg film-coated tablets. The procedure was finalised on 29 September 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
USP	United States Pharmacopoeia

I. INTRODUCTION

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

The product is indicated for:

- 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.
- adult and paediatric 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 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 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.

A comprehensive description of the indications and posology is given in the SmPC.

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

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

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

II. QUALITY ASPECTS

II.1 Introduction

Imatinib Aenorasis 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.

Imatinib Aenorasis 100 mg is a dark yellow to brownish-orange, round shaped, film-coated tablet with a break-line on one side and '100' on the other side. The tablet can be divided into equal doses.

Imatinib Aenorasis 400 mg is a dark yellow to brownish-orange, ovaloid shaped, film-coated tablet with a break-line on one side and '400' on the other side. The tablet can be divided into equal doses.

The film-coated tablets are packed in PVC/PE/PVDC/Alu blisters.

The excipients are:
Tablet core - microcrystalline cellulose (E460), low substituted hydroxypropyl cellulose (E463), povidone (E1201), crospovidone (Type A) (E1201), colloidal anhydrous silica (E551), magnesium stearate (E572)
Coating - hypromellose (E464), macrogol 400, talc (E553b), red iron oxide (E172), yellow iron oxide (E172).

The two strengths are dose proportional.

II.2 Drug Substance

The active substance is imatinib mesilate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a white to off-white to brownish or yellowish tinged crystalline powder, which is freely soluble in water, slightly soluble in ethanol, practically insoluble in methylene chloride. The drug substance is produced in one polymorph form (Alpha Form).

The Active Substance Master File (ASMF) procedure is used for both manufacturers of 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
One ASMF holder produces imatinib mesilate in a 3 step chemical reaction followed by a final step of milling. The other ASMF holder uses 6 steps for the synthesis. Both manufacturing processes are adequately described. Starting materials, intermediates, and reagents used have been sufficiently specified.

Quality control of drug substance
Adequate drug substance specifications have been laid down. Batch analysis results for 4 batches (manufacturer-I) and 3 batches (manufacturer-II) have been provided, meeting the set requirements.

Stability of drug substance
For the first manufacturer, stability data on the active substance have been provided for four batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). Based on the available stability data a retest period of 2 years can be granted, without the need for a specific storage condition. Therefore the proposed storage condition below 25°C is considered not required, yet no objection.

Sufficient stability results for the process of the second manufacturer are available to support the claimed retest period of 24 months without specific storage temperature condition based on 6 months accelerated and 24 months normal stability data for 3 batches. All stability results meet the current drug substance specification.

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 and functions of the various excipients have been sufficiently described. The manufacturing process development has been justified. Breakability of both tablet strengths has been demonstrated in accordance with Ph.Eur. requirements.

A bioequivalence study has been performed with the 400 mg product strength versus its respective reference product. The 400 mg batch used in the bioequivalence study was manufactured according to the finalized composition and manufacturing process. Sufficient comparative dissolution data between the test and reference product have been provided.

For the 100 mg product a biowaiver was justified. The biowaiver is based on the bioequivalence study with the 400 mg product. Both batches comply with the general biowaiver criteria and it has been sufficiently demonstrated that dissolution of the 100 mg batch is similar to that of the 400 mg bioequivalence study test batch under the relevant dissolution conditions (0.1N HCl, pH 4.5 and pH 6.8). The 100 mg and 400 mg film-coated tablets are fully dose proportional tablets and are manufactured using the same manufacturing process.
The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process comprises the following steps: weighing of materials, preparation of the granulation solution, granulation, drying and sieving, blending, lubrication, compression, coating and packaging. The manufacturing process – a straightforward process based on wet granulation – has been adequately described. Process validation has been performed for three batches of both the 100 mg and the 400 mg manufacturing processes.

Control of excipients
All excipients comply with the respective Ph.Eur. monographs. The excipient Low Substituted Hydroxypropyl Cellulose and the colourants red iron oxide (E172) and yellow iron oxide (E172) are in accordance with the United States Pharmacopoeia (USP) and Directive 2012/231/EU. These specifications are acceptable.

Quality control of drug product
Drug product specifications are applied on description, identification of imatinib, identification of mesilate counter ion, identification of ferric oxides, dimensions, assay, related substances, residual ethanol, dissolution, uniformity of dosage units, water content, uniformity of mass, subdivision of tablets, and microbiological examination. All analytical methods have been adequately described. All

other drug product specifications can be accepted. Batch results are provided for the three validation batches per strength as well as a smaller batch per strength from manufacturer-1 and 5 batches per strength from manufacturer-2. All results met the set requirements.

Stability of drug product
Five validation batches of each strength, as well as a smaller batch per strength, have been stored at 25°C/60% RH up to 24 months and 40°C/75% RH for 6 months. All stability results met the set shelf-life requirements, and no clear trends have been observed. Photostability testing showed that the tablets are not sensitive to light.
Based on the available stability data the claimed shelf-life of 3 years in the proposed blister packaging without specific storage condition can be granted.

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 Aenorasis 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 Aenorasis 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, which is 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 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 the test product Imatinib Aenorasis 400 mg film-coated tablets (Aenorasis S.A., Greece) is compared with the pharmacokinetic profile of the reference product Glivec 400 mg film-coated tablets (Novartis Europharm Limited, UK).

The choice of the reference product

The choice of the reference product in the bioequivalence study is accepted, 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

A biowaiver has been granted for the 100 mg strength, based on the result of the bioequivalence study conducted with the 400 mg strength, with the following justification:

- Imatinib 100 mg & 400 mg tablets are manufactured by the same manufacturer using the same manufacturing process.
- The qualitative composition of the 100 mg tablets is the same as that of the 400 mg tablets
- Imatinib 100 mg tablets are dose proportional with imatinib 400 mg tablets. Thus, the ratio between the amount of each core excipient to the amount of active substance is the same for both the strengths.
- Imatinib pharmacokinetics has been shown to be linear between 25 and 1000 mg in patients with chronic-phase (CP) CML or advanced-phase CML or acute leukaemia.
- The dissolution profiles of imatinib 100 mg tablets are similar to the 400 mg tablets.

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 30 healthy volunteers (21 non-smoking males, 9 post-menopausal and/or surgically sterile females), aged 21-68 years. Each subject received a single dose (400 mg) of one of the 2 imatinib formulations. The meal consisted of 2 eggs, 2 slices of toast, 136 g of hash brown potatoes, 240 ml whole milk, 2 slices of bacon and 2 tablespoons of butter (total 910.8 kcal). There were 2 dosing periods, separated by a washout period of 14 days.

Blood samples were collected pre-dose and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 7.0, 8.0, 10, 12, 18, 24, 36, 48, 72 and 96 hours after administration of the products.

The single-dose study design is acceptable. Since imatinib has to be administered with a meal in order to avoid gastrointestinal irritation, the administration under fed conditions is agreed. The dosing schedule is adequate and the washout period is considered sufficient.

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

Three subjects dropped out prior to period 2, due to personal reasons, due to adverse events or due to out-of-range of creatinine and creatinine clearance levels. Pharmacokinetic and statistical analysis was conducted using data obtained from 27 subjects completing both study periods.

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

Treatment N=27	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h
Test	34434 ± 12177	35372 ± 12390	1900 ± 635	5.0 (2.0-8.0)
Reference	36231 ± 12127	37081 ± 12357	2031 ± 634	4.0 (2.0-10.0)

***Ratio (90% CI)**	0.95 (0.89-1.00)	0.95 (0.90-1.01)	0.93 (0.87-0.99)	--
CV (%)	12.81	12.33	13.56	--

$AUC_{0-\infty}$ 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

**ln-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80-1.25. Based on the pharmacokinetic parameters of imatinib under fed conditions, it can be concluded that Imatinib Aenorasis 400 mg film-coated tablets and Glivec 400 mg film-coated tablets are bioequivalent.

There were 23 adverse events (AEs) involving 13 subjects in this study No serious AEs were reported. 11 AEs were associated with 7 subjects receiving the test formulation, and 11 AEs in 9 subjects receiving the reference formulation.

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 Aenorasis.

Summary table of safety concerns as approved in RMP

Important identified risks	• Hypothyroidism • Hepatotoxicity • Edema and Fluid retention • Central Nervous System (CNS} and • Gastrointestinal (GI) haemorrhage • Tumour lysis syndrome • Myelosuppression • Growth retardation in children • Cardiac failure • Hypophosphataemia • Severe respiratory adverse reactions • Rhabdomyolysis and Myopathy • Acute Renal Failure • Gastrointestinal Obstruction, Perforation, or Ulceration • Skin Rashes and Severe Cutaneous Reactions • Ovarian Hemorrhage and Hemorrhagic Ovarian Cyst • Interaction with strong CYP3A4 inhibitors, strong CYP3A4 inducers and drugs eliminated by CYP3A4

Important potential risks	• Hypoglycaemia
	• Second Malignancies in survivors
	• Tolerability during pregnancy and pregnancy outcomes
	• Disseminated intravascular coagulation
	• Suicidality
	• Interaction with:
	  ◦ Drugs eliminated by CYP2C9, CYP2C19 and CYP2D6.
	  ◦ Acetaminophen/paracetamol

Missing information	• Long term follow up in pediatric patients • Pediatric 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 100 mg and 400 mg film-coated tablets. 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 procedure NL/H/3008/01-02/DC, and original procedure NL/H/2540/001-002/DC. The reference product concerns Imatinib. The bridging report submitted by the MAH has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Imatinib Aenorasis 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.

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 Aenorasis 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 29 September 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