CBG MEB

Public Assessment Report

Scientific discussion

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

(imatinib)

NL/H/2987/001-002/DC

Date: 29 September 2015

This module reflects the scientific discussion for the approval of Imatinib Hetero 100 mg and 400 mg, film-coated tablets The procedure was finalised on 21 August 2014. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

I. INTRODUCTION

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

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 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 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 by Novartis Europharm Limited, which have been registered in the EEA through a centralised procedure since 7 November 2001 (100 mg) and 11 November 2003 (400 mg) (EU license number EU/1/01/198).

The concerned member states (CMS) involved in this procedure were Denmark, Germany, Spain and Sweden.

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

II. QUALITY ASPECTS

II.1 Introduction

Imatinib Hetero 100 mg is a brownish orange coloured, round, bevel edged scored tablet debossed with H on one side and 19 on the other side, 1 and 9 separated by a score line. The tablet can be divided into equal doses.
Imatinib Hetero 400 mg is a brownish orange coloured, capsule shaped, bevel edged scored, film-coated tablet debossed with H on one side and 20 on the other side, 2 and 0 separated by a score line. The tablet can be divided into equal doses.

The film-coated tablets are packed in Aluminium/Aluminium blisters and HDPE containers with polypropylene cap and silica gel desiccant.

The excipients are:
Tablet core - magnesium stearate
Tablet coating - hypromellose (E464), titanium dioxide (E171), yellow iron oxide (E172), red iron oxide (E172), talc (E553b), macrogol (E1521)

The two strengths are dose proportional.

II.2 Drug Substance

The active substance is imatinib mesilate, an established active substance not described in the European Pharmacopoeia (Ph.Eur.). It is an off-white to brownish yellow colour powder, which is freely soluble in water. The active substance exhibits pH dependent solubility. Solubility decreases with increasing pH. The active substance has no asymmetric carbons. The drug substance is produced in one polymorph form (Alpha Form).

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.

<u>Manufacturing process</u>

Five starting materials are used in the process, which involves six stages. The manufacturing process starting from these materials is sufficiently detailed described, including all experimental conditions and in-process controls. Polymorphic form alpha is consistently manufactured, and has also been demonstrated to be stable in drug substance and drug product.

Quality control of drug substance
The drug substance specification of the MAH is identical to the drug substance specification of the ASMF holder with some additional tests (bulk density and microbiological purity). The proposed drug substance specification limits are acceptable. Batch analysis results for 3 batches have been provided, demonstrating compliance with the set requirements.

Stability of drug substance
Stability data on the active substance have been provided for three production-scale batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months) and 30°C/65%RH (12 months). No significant changes were observed in the currently available stability data. Based on the provided stability data, the proposed re-test period of 48 months is acceptable. The drug substance is photostable.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The qualitative composition of the generic product differs from that of the reference product. The dissolution is, however, similar, for both the tablet strengths. Manufacturing process development is adequately explained and concerns a standard process.
A bioequivalence study was carried out with the 400 mg strength. The dissolution profiles obtained of the test and reference product were similar at pH 1 and pH 4.5. At pH 6.8 there was a minor difference. Bioequivalence was shown. A biowaiver was requested for the 100 mg strength. The biowaiver is acceptable, considering the quantitative proportional compositions and the similar dissolution profiles of the 100 mg and 400 mg strength of the generic product across the physiological pH range. Breakability of both tablet strengths has been demonstrated in accordance with Ph. Eur. requirements.

Manufacturing process
The manufacturing process includes dry blending, compression, and film-coating. The manufacturing process is regarded as a standard process. The description of the manufacturing process is sufficiently detailed. The process has been sufficiently validated. Process evaluation data were presented for two batches of each strength at semi industrial batch size. All batches complied with the predefined acceptance criteria. Acceptable process validation protocols have been provided for the next production batches after product approval.

Control of excipients
All individual excipients comply with the Ph.Eur. or USP-NF where relevant. The specifications of the excipients are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identification, ferric oxide identification, average weight, loss on drying, dissolution, uniformity of dosage units, degradation products, assay, and microbial limits. The proposed drug product specification is acceptable with regard to the release and shelf-life limits. The dissolution rate is sufficiently tight, and is in conformity with dissolution of the biobatch results (rapid dissolution). The limits for degradation products are qualified, and sufficiently tight. Analytical methods are adequately described, and have been sufficiently validated.
Batch analysis data showing compliance with the proposed release specification have been provided for two of each strength.

Stability of drug product
Stability data on the product was provided for two batches of each strength at semi-industrial size stored at 25°C/60% RH (24 months), 40°C/75% RH (6 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 packages.
No significant changes were observed. Levels of all other degradation products remained below the reporting threshold at both storage conditions. Photostability has been demonstrated. Based on the provided stability data, the proposed shelf life of 36 months is approvable, without special storage conditions.

An in-use stability study has been performed with the tablet container stored at 25°C /60%RH (long term) and tested for 90 days at an interval of 30, 60 and 90 days. No significant changes were observed during the 90 days tested period.

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 Hetero 100 mg and 400 mg, film-coated have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:

- The MAH committed to provide the updated ASMF applicant's part including all approved drug substance data.
- The comparative dissolution profiles in different media (pH 1 to 6.8) for the first three production batches of 400 mg tablet strength complying with the dissolution profile of the biobatch will be generated.
- The MAH committed to submit the results of the on going stability studies of the product up to the shelf-life.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Imatinib Hetero 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

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Imatinib Hetero 400 mg (Hetero Europe S.L., Spain) is compared with the pharmacokinetic profile of the reference product Glivec 400 mg film-coated tablets (Novartis Europharm Ltd, UK).

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

The MAH provided a justification for the biowaiver of conduction bioequivalence studies with the lower 100 mg tablet strength based on the bioequivalence study for the 400 mg tablet strength.
Both strengths are manufactured by the same manufacturing process and the qualitative/quantitative (proportional) composition is the same.
Furthermore, comparative dissolution between the 100 mg and 400 mg test tablets was demonstrated in 4 different media. As all criteria from the guideline on the investigation of bioequivalence regarding a biowaiver for strengths have been met, the biowaiver for the lower strength has been granted.

Bioequivalence studies

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 36 healthy male subjects, aged 20-44 years. Each subject received a single dose (400 mg) of one of the 2 imatinib formulations. Subjects were fasting overnight and were served a high fat high calorie breakfast. The breakfast should be finished within 30 minutes and the dose was administered, with 240 mL water, 30 minutes after the start of the breakfast. The total caloric content of the breakfast was 938 Kcal, of which 28% carbohydrate, 58% fat and 15% protein. There were 2 dosing periods, separated by a washout period of 8 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 single-dose study design is acceptable. The length of the sampling period was sufficient as well as the sampling frequent to estimate the expected pharmacokinetic parameters. Since imatinib has to be administered with a meal in order to avoid gastrointestinal irritation, the administration under fed conditions is agreed.

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

One subject dropped out of the study in the first period, due to an adverse event (loose stool). A total of 33 subjects were included in the statistical analysis of the AUC and a total of 35 subjects were included in the statistical analysis of the C_{max}. For 2 subjects AUC_{0-t} , $AUC_{0-\infty}$, $t_{1/2}$, λ_z, $AUC_{\_\%Extrap\_obs}$ were not determined as both had 3 consecutive missing samples in the elimination phase.

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

Treatment	**AUC_{0-t} n=33** µg.h/ml	**$AUC_{0-\infty}$ n=33** µg.h/ml	**C_{max} n=35** µg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	35.2 ± 11.9	36.9 ± 12.7	1.9 ± 0.6	3.0 (1.5-6.0)	--

Reference	34.8 ± 12.3	36.5 ± 13.1	1.9 ± 0.6	3.67 (2.0-8.0)	--
***Ratio (90% CI)**	1.02 (0.97-1.07)	1.02 (0.97-1.07)	0.99 (0.94-1.05)	--	--
CV (%)	--	--	--	--	--

$AUC_{0-\infty}$ 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

**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 Hetero 400 mg is considered bioequivalent with Glivec 400 mg film-coated tablets.

During the study, only 2 adverse events were reported. These pertained:
- Diarrhoea, 3 hours after administration of the reference formulation and
- for one subject, eosinophilia, 72 hours after administration of the test product.

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 Hetero.

- Summary of Safety Concerns and Planned Risk Minimisation Activities as approved in RMP

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Identified Risk		
Myelosuppression	SmPC sections 4.2, 4.4, 4.8 and 5.3	N/A
Oedema and fluid retention	SmPC sections 4.4 and 4.8	N/A
GI and CNS haemorrhage	SmPC sections 4.4 and 4.8	N/A
GI ulceration, perforation and obstruction	SmPC section 4.8	N/A
Hepatotoxicity	SmPC sections 4.2, 4.4, 4.5, 4.8, 5.2 and 5.3	N/A
Skin Rashes and severe cutaneous reactions	SmPC section 4.8	N/A
Hypothyroidism	SmPC sections 4.4 and 4.5	N/A
Hypophosphatemia	SmPC section 4.8	N/A

Cardiac failure	SmPC sections 4.4 and 4.8	N/A
Renal failure	SmPC sections 4.2, 4.4, 4.8, 5.2 and 5.3	N/A
Severe respiratory adverse reactions	SmPC section 4.8	N/A
Rhabdomyolysis and myopathy	SmPC section 4.8	N/A
Ovarian haemorrhage and haemorrhagic ovarian cyst	SmPC section 4.8	N/A
Tumour lysis syndrome	SmPC sections 4.4 and 4.8	N/A
Growth retardation in children	SmPC sections 4.4 and 4.8	N/A
Interaction with strong CYP3A4 inhibitors	SmPC sections 4.4 and 4.5	N/A
Interaction with strong CYP3A4 inducers	SmPC sections 4.4 and 4.5	N/A
Interaction with drugs eliminated by CYP3A4	SmPC sections 4.4 and 4.5	N/A
Important potential risks		
Second Malignancies in Survivors	SmPC section 5.3	N/A
Disseminated intravascular coagulation	No risk minimization activities are proposed at this time	N/A
Hypoglycaemia	No risk minimization activities are proposed at this time	N/A
Suicidality	No risk minimization activities are proposed at this time	N/A
Tolerability during Pregnancy and Pregnancy outcomes	SmPC sections 4.6 and 5.3	N/A
Interaction with drugs eliminated by CYP2C9, CYP2C19 and CYP2D6	SmPC sections 4.5 and 5.2	N/A
Interaction with acetaminophen/paracetamol	SmPC section 4.4	N/A
Missing information		
Pediatric Patients: Long term Follow up	SmPC section 4.4	N/A
Pediatric patients below 2 years of age	SmPC section 4.2	N/A
Renal impairment	SmPC sections 4.2 and 4.4 and 5.2	N/A

Hepatic impairment	SmPC sections 4.2 and 4.4 and 5.2	N/A
Elderly patients	SmPC section 4.2	N/A

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

The package leaflet (PL) has not been evaluated via a user consultation study. Based upon similarities in the textual content, format, design, layout and wording of the PLs, along with an analysis of the key safety messages, the PL for Imatinib Hetero film-coated tablets meets the necessary guidance for being bridged to Glivec film-coated tablets. The bridging has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Imatinib Hetero 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 Hetero 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 21 August 2014.

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