2 August 2013
EMA/622006/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Imatinib medac

International non-proprietary name: IMATINIB

Procedure No. EMEA/H/C/002692/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

CAS Chemical Abstract Service

NMT Not more than

TAMC Total aerobic microbial count

TYMC Total Yeasts and mould count

DMF: Dimethylformamide

IPA: Isopropyl alcohol

LOD: Limit of Detection

LOQ: Limit of Quantification

mg: Milligram

µg/mL: Parts per million

mg/mL: Milligram per Milliliter

MOA : Method of Analysis

µ : Micron

µm : Micrometer

µL : Micro liter

mm : Millimeter

min : Minute

mL : Milliliter

mL/min : Milliliter per minute

NA : Not Applicable

NLT : Not Less Than

nm : Nanometer

NMT : Not More Than

Sr. No. : Serial Number

PVC/PVDC/Alu: polyvinylchloride/polyvinylidene chloride/aluminium

QA : Quality Assurance

RT : Retention time

UV : Ultra-Violet

v/v : Volume by volume

w.r.t. : With respect to

% : Percentage

°C : Degree Celsius

1. Background information on the procedure

1.1. Submission of the dossier

The Applicant Medac submitted on 28 September 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Imatinib medac, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 27 January 2012.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product for which a Marketing Authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The Applicant applied for the following indications:

- 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 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.
- Adult patients with unresectable dermatofibrosarcoma protuberans (DFSP) and adult patients
- with recurrent and/or metastatic DFSP who are not eligible for surgery.

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

In adult and paediatric patients, the effectiveness of Imatinib medac 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 DFSP. The experience with Imatinib medac in patients with MDS/MPD associated with PDGFR gene rearrangements 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.

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Glivec instead of non-clinical and clinical data unless justified otherwise.

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Not applicable

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the Applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

The chosen reference product is:

■ Medicinal product which is or has been authorised in accordance with Community in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Glivec 100 mg hard capsules, Glivec 400 mg film-coated tablets
- Marketing authorisation holder: Novartis Europharm Limited, UK
- Date of authorisation: 27-11-2001
- Marketing authorisation granted by: Community
- Community Marketing authorisation number:
  For 100 mg: EU/1/01/198/002-006
  For 400 mg: EU/1/01/198/009

■ Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Glivec 100 mg hard capsules, Glivec 400 mg film-coated tablets
- Marketing authorisation holder: Novartis Europharm Limited, UK
- Date of authorisation: 27-11-2001
- Marketing authorisation granted by: Community
- Community Marketing authorisation number:
  For 100 mg: EU/1/01/198/002-006
  For 400 mg: EU/1/01/198/009

■ Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

Product name, strength, pharmaceutical form: Glivec 400 mg film-coated tablets

- Marketing authorisation holder: Novartis Europharm Limited
- Date of authorisation: 27-11-2001
- Marketing authorisation granted by: Community

- Community Marketing authorisation number: EU/1/01/198/010
- Bioavailability study number(s): IMA-BIO-01-11

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturers responsible for batch release

medac Gesellschaft fuer Spezialpraeparaten mbH

Theater strasse 6
22880 Wedel
GERMANY

Pabianickie Zaklady Farmaceutyczne Polfa S.A.
ul. Marszalka J. Pilsudskiego 5
95-200 Pabianice
Poland

1.3. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: John Joseph Borg

- The application was received by the EMA on 28 September 2012.
- The procedure started on 24 October 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 11 January 2013.
- During the meeting on 21 February 2013, the CHMP agreed on the consolidated List of Questions to be sent to the Applicant. The final consolidated List of Questions was sent to the Applicant on 22 February 2013.
- The Applicant submitted the responses to the CHMP consolidated List of Questions on 23 May 2013.
- The Rapporteur circulated the Assessment Report on the Applicant's responses to the List of Questions to all CHMP members on 24 June 2013.
- The Rapporteur submitted an amended Assessment Report on the Applicant's responses to the List of Questions to all CHMP members on 24 July 2013.
- During the meeting on 25 July 2013, the CHMP discussed the application. In the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Imatinib medac via written procedure on 2 August 2013.
- The CHMP adopted a report on similarity of Imatinib Medac (imatinib) with Tasigna (nilotinib), Sprycel (dasatinib), Vidaza (azacitidine), Evoltra (clorafabine), Atriance (nelarabine), Xaluprine

(mercaptopurine), Bosulif (bosutinib), Iclusig (ponatinib) and Revlimid (lenalidomide) on 2 August 2013.

2. Scientific discussion

2.1 Introduction

Imatinib medac, 100 mg and 400 mg hard capsules is a generic medicinal product of Glivec which has been authorised in the EU since 07/11/2001.

The active substance of Imatinib medac is imatinib (as mesilate), it is a protein-tyrosine kinase inhibitor (ATC code: L01XE01) that potently inhibits the activity of the Bcr-Abl tyrosine kinase (TK), as well as several receptor tyrosine kinases.

The safety and efficacy profile of imatinib has been demonstrated in several clinical trials details of which can be found in the EPAR for Glivec. In addition, there is extensive post-marketing experience contributing to the knowledge of the clinical use of this product. Since this application is a generic application referring to the reference medicinal product Glivec, summary of the clinical data of imatinib is available and no new clinical studies regarding pharmacology, pharmacokinetics and efficacy and safety have been conducted.

The Applicant has demonstrated bioequivalence with the reference medicinal product Glivec. To support the marketing authorisation application, the Applicant conducted one bioequivalence study with cross-over design under fed conditions. This study was the pivotal study for the assessment.

The Applicant applied for the following indications:

- 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.
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on objective response rates in adult patients with unresectable and/or metastatic DFSP. The experience with Imatinib medac in patients with MDS/MPD associated with PDGFR gene rearrangements 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.

Imatinib medac is presented as hard gelatine capsules in two strengths; 100 and 400 mg, whereas the reference medicinal product Glivec is available in three strengths; 50mg, 100 mg and 400 mg and the two highest strengths are not only available as capsules but also as film-coated tablets.

The Imatinib medac pack sizes are consistent with the dosage regimen and duration of use.

2.2 Quality aspects

2.2.1 Introduction

The finished product is presented as hard capsules containing 100 mg or 400 mg of imatinib (as mesilate) as the active substance.

Other ingredients are:

Capsule filling
Crospovidone (type A)
Lactose monohydrate
Magnesium stearate

Capsule shell
Gelatin
Yellow iron oxide(E172)
Titanium dioxide(E171)
Red iron oxide (E172)
Black iron oxide(E172)

The product is available in blisters made of PA-aluminium-PVC laminate and an aluminium foil as described in section 6.5 of the SmPC.

2.2.2 Active substance

The chemical name of imatinib (INN) as the mesilate salt is 4-[(4-methyl-1-piperazinyl) methyl]–N–[4-methyl-3-[[4-(3- pyridinyl)-2-pyrimidinyl]amino]-phenyl]-benzamide methane sulfonate salt .

Imatinib mesilate is a white to off-white crystalline powder, slightly hygroscopic, freely soluble in water, 0.1 M HCl, acetate buffer (pH=4.5), soluble in methanol, slightly soluble in ethanol, chloroform, and very slightly soluble in dichloromethane and phosphate buffer (pH=6.8). It has a non-chiral molecular structure. Exhibits polymorphism and its most thermodynamically stable polymorphic form has been determined and the crystallisation process is designed to consistently deliver this form

The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure.

Manufacture

Imatinib mesilate is synthesized in 5 main steps where imatinib is first produced followed by its transformation into the mesilate salt. The starting materials are well defined and commercially available. It is supplied by one active substance manufacturer.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented and found acceptable.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set. The potential formation of genotoxic impurities is addressed in the active substance specification.

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Specification

The active substance specification includes tests for appearance, identity (IR, HPLC), assay (HPLC) related substances (HPLC), genotoxic impurities (LC-MS/MS, HPLC), polymorphism (XRPD), melting point (DSC), water content (KF), heavy metals (Ph.Eur.), sulphated ash (Ph.Eur.), residuals solvents (GC) and microbiological purity (Ph.Eur.).

The presence of genotoxic impurities in the specification raises no concerns as its potential formation has been addressed by the Applicant and batch analysis data for the drug substance comply with specification.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

Batch analysis data are provided on three pilot scale batches produced with the proposed synthetic route, and the batch analysis data show that the active substance can be manufactured reproducibly.

Stability

Three production scale batches of the active substance packed in the intended commercial packaging from the proposed manufacturer were put on stability testing as per ICH conditions: under long term (25°C/60%RH) for up to 18 months and accelerated (40°C/75%RH) for up to 6 months.

A photostability test following ICH guidelines Q1B was performed on one single batch and results under stress conditions (acidic and alkaline environment, impact of H_2O_2, impact of high temperature) were also provided for one batch.

The following parameters were tested: appearance, identification (IR and HPLC), related substance (HPLC, XRPD), water content (KF), melting point (DSC) and assay (HPLC). The HPLC method demonstrated to be stability indicating.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

2.2.3 Finished medicinal product

Pharmaceutical development

Imatinib medac hard gelatin capsules contain 100 or 400 mg of imatinib mesilate.

The intention during the pharmaceutical development was to obtain a stable formulation essentially equivalent to the reference medicinal product Glivec 100 mg, 400 mg film-coated tablets. The development studies were mainly performed in imatinib 400 mg hard capsules; the 100 mg hard capsules were developed to be dose proportional to the 400 mg capsules.

All the characteristics of the reference formulation and active substance were taken into consideration.

The composition of the initial blend was similar to that of the reference tablet formulation.

The formulation proposed for marketing contains the following excipients: crospovidone, lactose monohydrate and magnesium stearate. The capsule shell contains gelatin, titanium oxide, yellow iron oxide, red iron oxide and black iron oxide (colorants). All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation.

The compatibility of the active substance with these excipients was demonstrated during stability studies program.

The difference in excipients between Imatinib medac hard capsules and the reference medicinal product Glivec (hard capsules or film-coated tablets) is not considered significant for the safety, efficacy and performance of the medicinal product. The Imatinib medac product information contains an appropriate warning about the presence of lactose.

The Applicant performed a bioequivalence study on the 400 mg hard capsule and requested a biowaiver for the 100 mg strength. Exemption of a bioavailability study for the 100 mg strength was acceptable since all requirements of a biowaiver for this strength have been fulfilled. A comparative dissolution study has been performed to support the biowaiver. The discriminatory power of the dissolution method has been demonstrated.

The impurity profile of Imatinib medac has been compared with that of Glivec. Results indicate that there is no significant difference between impurities profiles of Imatinib medac 100 mg, 400 mg hard capsules and Glivec 100 mg, 400 mg film-coated tablets

The primary packaging proposed is PA-aluminium-PVC laminate blisters with an aluminium foil. The material complies with the European requirements and it is adequate to support the stability and use of the product.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

Gelatin is obtained from bovine/limed bone is used in the product. Valid TSE CEP from the suppliers of the gelatin used in the manufacture is provided.

Manufacture of the product

The manufacturing process consists of six main steps: weighting, mixing, roller compaction, blending, encapsulation and packaging.The process is considered to be a standard manufacturing process.

The process is a simple dry granulation, encapsulation and packaging process.

The manufacturing process has been adequately described.

The in process controls are adequate for this pharmaceutical form. The batch analysis data on two pilot scale batches shows that the capsules can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of this oral preparation. The Applicant has provided an adequate validation scheme and the manufacturing process will be validated prior to marketing on three validation batches.

Product specification

The finished product release specification include appropriate tests for appearance, identity of the active substance (HPLC, UV), assay (HPLC), uniformity of dosage units (Ph.Eur.), related substances (HPLC), dissolution (HPLC), water content and microbiological purity.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

Batch analyses results are provided for 6 production scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data for two production scale batches of each strength, stored under long term conditions (25ºC/60%RH) for up to 36 months and stored under accelerated conditions (40ºC/75%RH) for up to 6 months, according to the ICH guidelines, have been provided. In addition, up to 12 months stability data have been provided generated under intermediate conditions (30ºC/65%RH). Furthermore, two batches were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products.

The package used for the stability studies is the same as the one proposed for marketing. The samples were tested for appearance, assay (HPLC), related substances (HPLC), dissolution (HPLC) and microbiological purity. Microbiological purity of the finished product is tested at the beginning and at the end of the studies what is acceptable. The analytical procedures used were stability indicating.

The obtained results show that medicinal product is chemically and physically stable for 6 months in this the proposed packaging material at long term and accelerated conditions. Additionally, the photostability study shows that product is not light sensitive. The container for the finished product is selected properly and does not cause any incompatibility. Based on available stability data, the proposed shelf-life and storage conditions as stated in the SmPC are acceptable.

2.2.4 Discussion on chemical and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and

uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

The presence of genotoxic impurities in the active substance specification raises no concerns as its potential formation has been addressed by the Applicant and batch analysis data for the drug substance and the finished product comply with specification.

Although Imatinib medac contains different excipients compared to the reference medicinal product, it is considered not to affect its performance in the clinic. An adequate warning for lactose has been included in the product information.

2.2.5 Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6 Recommendation(s) for future quality development

Not applicable

2.3 Non-clinical aspects

2.3.1 Introduction

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. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2 Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the Applicant as the introduction of Imatinib medac manufactured by medac is considered unlikely to result in any significant increase in the combined sales volumes for all imatinib containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

2.3.3 Discussion and conclusion on non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of imatinib are well known. No non-clinical data are submitted with this application. Published literature has been reviewed and is considered of suitable quality.

In line with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00), justification for not providing ERA is acceptable.

2.4 Clinical aspects

2.4.1 Introduction

This is an application for hard capsules containing imatinib (as mesilate) in two different strengths 100 and 400 mg. To support the marketing authorisation application, the Applicant conducted one bioequivalence study with cross-over design under fed conditions. This study was the pivotal study for the assessment.

The Applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of imatinib based on published literature. The SmPC is in line with the SmPC of the reference product for the indications applied for by the Applicant.

No CHMP scientific advice pertinent to the clinical development was given for this medicinal product. For the clinical assessment the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1/Corr**) is of particular relevance.

GCP

The clinical trial was performed in accordance with GCP as claimed by the Applicant.

Exemption

A biowaiver for the formulation of the lower strength (100 mg) has been applied for based on dissolution profiles. The different hard capsules strengths are manufactured with the same process and by the same manufacturer. They have the same qualitative composition and a proportional quantitative composition.

Dissolution profiles were performed in 0.1 M HCl, Buffer pH 4.5 and in buffer pH 6.8. Dissolution profiles for Glivec film-coated tablets and for imatinib hard capsules were performed in Ph Eur. apparatus 2 with sinkers in 900 ml of dissolution medium with rotation speed of 50 rpm.

The dissolved amount of imatinib hard capsules 100 and 400 mg and from Glivec film-coated capsules 100 and 400 mg is above 85% in 0.1M HCl, as well as in buffer pH 4.5 and pH 6.8 with the exception of Glivec 100mg (batch: S0100) at pH 6.8 (about 77%)

This evidence is sufficient to grant a biowaiver for the proportional formulations of lower strengths, also considering the linear PK of imatinib in the dose range of 25 to 1000 mg.

Clinical studies

To support the application, the Applicant has submitted one bioequivalence study.

Table 1. Tabular overview of clinical study

Type of Study	Study Identifier	Location of Study Report	Objectives of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Patients	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status, Type of Report
Bioequivalence study	IMA-BIO-01-11	Module 5	The objectives of the study were as follows: - to evaluate the pharmacokinetic properties and investigate the bioequivalence of imatinib from a new test formulation (Imatinib 400 mg hard capsules) compared with the reference formulation (Glivec 400 mg film-coated tablets) following a single oral dose administration of 400 mg under fed conditions, - to evaluate the safety and tolerability of these formulations.	A single centre, single dose, randomized, open-label, two-period, 2-way cross-over study under fed conditions with a wash-out period of 14 days between each drug administration in each Treatment Period.	Single dose of Imatinib 400 mg hard capsule given orally.	36 subjects completed the whole study.	Healthy male and post-menopausal female subjects.	Single dose of investigational medicinal products (one 400 mg hard capsule of test drug and one 400 mg film-coated tablet of reference drug) were administered to subjects. The clinical part of the study lasted 83 days from the date of the first subject screened to date of the end of clinical part (from 03-Aug-2011 to 24-Oct-2011, respectively).	Finished, Clinical Study Report version 01 dated 21-Nov-2011.

2.4.2 Pharmacokinetics

Study IMA-BIO-01-11: A randomized, open-label, 2-way cross-over bioequivalence study comparing single dose of imatinib 400 mg (Imatinib 400 mg hard capsules vs Glivec 400 mg film-coated tablets) under fed conditions in healthy volunteers.

Methods

Study design

The study was a single centre, single dose, randomised, open-label, laboratory-blinded, two-period, 2-way cross-over under fed conditions with a wash-out period of 14 days between each drug administration in each treatment period.

Test and reference products

Test drug	Imatinib 400 mg hard capsule
Batch No.	030311-400B
Retest date	09.2011
Dose in the study	400 mg of imatinib (one hard capsule). Each hard capsule contains imatinib mesilate equivalent to 400 mg of imatinib free base.

Reference drug	Glivec 400 mg film-coated tablet
MAH	Novartis Europharm Limited
Manufacturer	Novartis Pharma GmbH
Batch No.	S0003B
Country of purchase	Germany
Expiry date	11.2013
Dose in the study	400 mg of imatinib (one film-coated tablet). Each film-coated tablet contains imatinib mesilate equivalent to 400 mg of imatinib free base.

Population(s) studied

Forty-one (41) healthy human male and post-menopausal female subjects, who met all of the inclusion and none of the exclusion criteria, were randomized but forty (40) subjects were dosed. Subjects were healthy, adult, males between 21 and 58 years of age (both inclusive) and females between 42 and 58 years of age (both inclusive), having a BMI between 18.5 to 27.99 kg/m^2 (both inclusive).

Analytical methods

The analytical method chosen in this study is LC-MS/MS as this was a suitable technique to achieve the proposed lower level of quantification (LLOQ) which was 20 ng/mL. Also noted that the assay was selective using LC-MS/MS and the quantification would be done based on the mass to charge ratio of molecule. The method validation report was provided by the Applicant.

Pharmacokinetic variables

The primary pharmacokinetics parameters considered for the assessment of BE were C_{max} and AUC_{0-t}.

The secondary pharmacokinetics parameters that were assessed were: $AUC_{0-\infty}$ T_{max}, residual area, λ_z and $t_{½}$.

Statistical methods

Statistical analysis was performed on the data obtained from subjects who completed both treatment periods of the study with no significant protocol deviations, using SAS Software (Version 9.2, SAS Institute Inc. USA). Therefore results for thirty-six (36) subjects were statistically evaluated.

The ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were subjected to Analysis of Variance (ANOVA) for imatinib. An F-test was performed to determine the statistical significance of the effects involved in the model at a significance level of 5 % (α = 0.05).

90% confidence intervals of two one-sided t-tests for the ratio of geometric means between the formulations were calculated for ln-transformed data of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for imatinib.

According to guideline and Study Protocol assumptions, if the 90% confidence interval of two one-sided t-tests for ratio of geometric means (test formulation over reference formulation) for both C_{max} and AUC_{0-t} of imatinib are included entirely in the acceptance range of 80.00- 125.00%, the test formulation (Imatinib) will be concluded as bioequivalent to the reference formulation (Glivec).

Results

Table 1. Descriptive statistics of Formulation means for imatinib (n=36)

Parameters (Units)	Mean ± SD (Un-transformed data)	
	Reference Product - R	Test Product -T
T_{max} (h)#	3.500 (1.500 - 8.000)	4.500 (1.000 - 8.000)
C_{max} (ng / mL)	1683.713 ± 533.5567	1652.309 ± 640.8319
AUC_{0-t} (ng*h / mL)	28133.255 ± 9507.8088	27788.544 ± 9762.7290
$AUC_{0-\infty}$ (ng*h / mL)	29684.575 ± 10736.7870	29233.031 ± 10380.0076
λ_z (1 / h)	0.044 ± 0.0094	0.042 ± 0.0079
$t_{½}$ (h)	16.687 ± 4.1853	16.922 ± 3.3720
AUC_%Extrap_obs (%)	4.655 ± 2.8743	4.797 ± 2.5433

 # - T_{max} is presented as Median (Min-Max) value

Table 2. Geometric least squares mean, ratios and 90 % confidence interval for imatinib (n= 36)

Parameters (Units)	(ln-transformed) Geometric least squares mean			90% confidence interval (parametric)
	Test Product -T	Reference Product - R	Ratio (T/R)%	
C_{max} (ng / mL)	1424.730	1661.412	85.8 %	81.35-90.39 %
AUC_{0-t} (ng*h / mL)	23301.278	27915.985	83.5 %	80.86-86.17 %
$AUC_{0-\infty}$ (ng*h / mL)	24683.478	28917.149	85.4 %	82.52-88.30 %

Safety data

The clinical part of the study was completed without deaths, serious adverse events (SAEs) and suspected unexpected serious adverse reaction (SUSAR). In the study twenty six (26) adverse events were reported in seventeen (17) subjects. The most commonly observed adverse event in this study was headache.

Conclusions

Based on the presented bioequivalence study Imatinib medac 400 mg hard capsules is considered bioequivalent with Glivec 400 mg film-coated tablets.

The results of study IMA-BIO-01-11 with 400 mg formulation can be extrapolated to the lower strength 100 mg, according to conditions in the Guidelines.

2.4.3 Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4 Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.5 Discussion on clinical aspects

The assessment of bioequivalence complies with the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**). The 90% confidence intervals for C_{max} and AUC_{0-t} fall entirely into the acceptance interval 80.00-125.00%. On the basis of these results, bioequivalence is considered demonstrated.

2.4.6 Conclusions on clinical aspects

The CHMP considers Imatinib medac 100 mg and 400 mg hard capsules approvable from the clinical point of view.

2.5 Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the Applicant fulfils the legislative requirements.

Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 1, the PRAC considers by consensus that the risk management system for imatinib (Imatinib medac) can be accepted as an updated risk management plan and satisfactory responses to the questions detailed in Section 4 have been submitted.

The proposed indications for Imatinib medac are:

Chronic myeloid leukaemia (CML)

- Paediatric patients with newly diagnosed Philadelphia chromosome (bcr-abl), positive (Ph+) 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 (IFN rapy, or in accelerated phase,
- Adult and paediatric patients with Ph+ CML in blast crisis.

Acute lymphoblastic leukaemia (ALL)

- Adult patients with newly diagnosed Philadelphia chromosome positive ALL (Ph+ ALL) integrated with chemotherapy,

– Adult patients with relapsed or refractory Ph+ ALL as monotherapy. Myelodysplastic/myeloproliferative diseases (MDS/MPD),

– Adult patients with MDS/MPD associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements.

Hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL)

– Adult patients with advanced hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL) with FIP1L1-PDGFRα rearrangement.

Dermatofibrosarcoma protuberans (DFSP)

– Treatment of adult patients with unresectable dermatofibrosarcoma protuberans (DFSP) and adult patients with recurrent and/or metastatic DFSP who are not eligible for surgery.

This advice is based on the following content of the Risk Management Plan:

Safety concerns

The Applicant identified the following safety concerns in the RMP:

Table 2.1 Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	- Myelosuppression - Oedema and fluid retention - Gastrointestinal haemorrhage - Cerebral haemorrhage - Gastrointestinal ulceration, perforation, obstruction - Hepatotoxicity - Skin rashes, severe cutaneous reactions - Hypothyroidism - Hypophosphatemia - Cardiac failure - Renal failure - Acute respiratory failure / pulmonary hypertension / pulmonary fibrosis - Rhabdomyolysis and myopathy - Growth retardation - Ovarian haemorrhage and haemorrhagic ovarian cyst
Important potential risks	- Treatment-related secondary malignancies - Disseminated intravascular coagulation - Hypoglycaemia - Suicidality - Tolerability during pregnancy and pregnancy outcomes
Missing information	- long-term follow up in paediatric patients - paediatric patients below 2 years of age - hepatic impairment

Summary of safety concerns	
	- renal impairment - elderly patients

The PRAC agreed.

Pharmacovigilance plans

The PRAC, having considered the data submitted, was of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Table 2.4: Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Myelosuppression	*Labelled in SmPC sections 4.2, 4.4, 4.5, 4.8 and 5.3*	*None*
Oedema and fluid retention	*Labelled in SmPC sections 4.4 and 4.8*	*None*
Gastrointestinal haemorrhage	*Labelled in SmPC section 4.8*	*None*
Cerebral haemorrhage	*Labelled in SmPC section 4.8*	*None*
Gastrointestinal ulceration, perforation, obstruction	*Labelled in SmPC section 4.8*	*None*
Hepatotoxicity	*Labelled in SmPC sections 4.2, 4.4, 4.5, 4.8, 5.2 and 5.3*	*None*
Skin rashes, severe cutaneous reactions	*Labelled in SmPC section 4.8*	*None*
Hypothyroidism	*Labelled in SmPC section 4.4, 4.5 and 4.8*	*None*
Hypophosphataemia	*Labelled in SmPC section 4.8*	*None*
Cardiac failure	*Labelled in SmPC sections 4.4 and 4.8*	*None*
Renal failure	*Labelled in SmPC sections 4.2, 4.4, 4.8, 5.2 and 5.3*	*None*
Acute respiratory failure / pulmonary hypertension / pulmonary fibrosis	*Labelled in SmPC section 4.8*	*None*
Rhabdomyolysis and myopathy	*Labelled in SmPC section 4.8*	*None*
Growth retardation	*Labelled in SmPC sections 4.4 and 4.8*	*None*
Treatment-related secondary malignancies	*Labelled in SmPC section 5.3*	*None*

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Disseminated intravascular coagulation	*None – should PhV activities uncover additional data risk minimisation measures will be developed*	*None*
Hypoglycaemia	*None – should PhV activities uncover additional data risk minimisation measures will be developed*	*None*
Ovarian haemorrhage and haemorrhagic ovarian cyst	*Labelled in SmPC section 4.8*	*None*
Suicidality	*None – should PhV activities uncover additional data risk minimisation measures will be developed*	*None*
Tolerability during pregnancy and pregnancy outcomes	*Labelled in SmPC section 4.6 and 5.3*	*None*

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

The CHMP endorsed this advice without changes.

PSUR submission

At the time of granting the marketing authorisation, the submission of periodic safety update reports is not required for this medicinal product. However, the marketing authorisation holder shall submit periodic safety update reports for this medicinal product if the product is included in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83 and published on the European medicines web-portal.

User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the Applicant and has been found acceptable as the Applicant declared that the content of package leaflet is the same as that of the reference product.

3. Benefit-risk balance

This application concerns a generic version of Imatinib hard capsules.

The reference product Glivec is indicated for leukaemia.

No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the Applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The bioequivalence study forms the pivotal basis with a single centre, single dose, randomised, open-label, two-period, 2-way cross-over study under fed conditions with a wash-out period of 14 days between each drug administration in each treatment period. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Imatinib medac met the protocol-defined criteria for bioequivalence when compared with the Glivec .The point estimates and their 90% confidence intervals for the parameters AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} were all contained within the protocol-defined acceptance range of 80.00 to 125.00%. Bioequivalence of the two formulations was demonstrated.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

4. Recommendation

The CHMP by consensus is of the opinion that Imatinib medac is not similar to Tasigna (nilotinib), Sprycel (dasatinib), Vidaza (azacitidine), Evoltra(clorafabine), Atriance(nelarabine), Xaluprine (mercaptopurine), Bosulif(bosutinib), Iclusig(ponatinib) and Revlimid(lenalidomide) within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000.

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Imatinib medac in the treatment of leukaemia is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal products subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

At the time of granting the marketing authorisation, the submission of periodic safety update reports is not required for this medicinal product. However, the marketing authorisation holder shall submit periodic safety update reports for this medicinal product if the product is included in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83 and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.