EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 April 2013
EMA/389694/2013
Committee for Medicinal Products for Human Use (CHMP)

Imatinib Accord

Imatinib

Procedure No. EMEA/H/C/002681

Assessment report for initial marketing authorisation application

Assessment report as adopted by the CHMP with all commercially confidential information 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 Accord Healthcare Ltd. submitted on 3 May 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for imatinib Accord, 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 for the treatment of:

- paediatric patients with newly diagnosed Philadelphia chromosome (bcr-abl) positive (Ph+) chronic myeloid leukaemia (CML) for whom bone marrow transplantation is not considered as the first line of treatment.

- paediatric patients with Ph+ CML in chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis.

- adult patients with Ph+ CML in blast crisis.

- adult 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 on the outcome of bone marrow transplantation has not been determined.

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 DFSP. The experience with imatinib in patients with MDS/MPD associated with PDGFR gene re-arrangements is very limited. 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

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 provisions in accordance with Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Glivec 100 mg film-coated tablets, Glivec 400 mg film-coated tablets
- Marketing authorisation holder: Novartis Europharm Limited, UK
- Date of authorisation: 07-11-2001
- Marketing authorisation granted by: Community
- Community Marketing authorisation number:
  For 100 mg: EU/1/01/198/007-08-11-12
  For 400 mg: EU/1/01/198/009-10-13

■ 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 film-coated tablets, Glivec 400 mg film-coated tablets

- Marketing authorisation holder: Novartis Europharm Limited, UK
- Date of authorisation: 07-11-2001
- Marketing authorisation granted by: Community
- Community Marketing authorisation numbers:
  For 100 mg: EU/1/01/198/007-08-11-12
  For 400 mg: EU/1/01/198/009-10-13

■ 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 400mg
- Marketing authorisation holder: Novartis Europharm Limited, UK
- Date of authorisation: 07-11-2001
- Marketing authorisation granted by: Community
  Community Marketing authorisation number: EU/1/01/198/010
  Member state source: Spain
- Bioavailability study number: 727-10

Scientific advice

Not applicable

Licensing status

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

1.2. Manufacturer

Manufacturer responsible for batch release

Accord Healthcare Limited

Sage House

319 Pinner road

North Harrow, Middlesex HA1 4HF

United Kingdom

1.3. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Arantxa Sancho-Lopez

- The application was received by the EMA on 3 May 2012.
- The procedure started on 20 June 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 11 September 2012.
- During the meeting on 18 October 2012, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 21 January 2013.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 1 March 2013.
- During the meeting on 25 April 2013, the CHMP, 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 Accord.

2. Scientific discussion

2.1. Introduction

Imatinib Accord 100 mg and 400 mg film-coated tablets is a generic medicinal product of Glivec, which has been authorised in the EU since 7 November 2001.

The active substance of Imatinib Accord is imatinib, a protein-tyrosine kinase inhibitor which potently inhibits the Bcr-Abl tyrosine kinase at the in vitro, cellular and in vivo levels. The compound selectively inhibits proliferation and induces apoptosis in Bcr-Abl positive cell lines as well as fresh leukaemic cells from Philadelphia chromosome positive CML and acute lymphoblastic leukaemia (ALL) patients.

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 a long-term 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.

A comparative bioequivalence study was performed between the test product Imatinib Mesylate Tablets 400 mg and Glivec 400 mg Tablets. Imatinib Accord was found to be bioequivalent to the reference product Glivec.

The approved indication is:
Imatinib Accord is indicated for the treatment of :

- paediatric patients with newly diagnosed Philadelphia chromosome (bcr-abl) positive (Ph+) chronic myeloid leukaemia (CML) for whom bone marrow transplantation is not considered as the first line of treatment.

- paediatric patients with Ph+ CML in chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis.

- adults 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 on the outcome of bone marrow transplantation has not been determined.

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 DFSP. The experience with imatinib in patients with MDS/MPD associated with PDGFR gene re-arrangements is very limited. There are no controlled trials demonstrating a clinical benefit or increased survival for these diseases.

2.2. Quality aspects

2.2.1. Introduction

The finished product Imatinib Accord is presented as 100 mg and 400 mg film-coated tablets containing imatinib as the active substance. The composition is described in section 6.1 of the SmPC.

The product is available in the following primary packaging PVC/PVdC/Alu blisters and Alu/Alu blisters as described in section 6.5 of the SmPC.

2.2.2. Active substance

The active substance imatinib (INN) presented as the mesilate or 4-[(4-methyl-1-piperazinyl) methyl]–N–[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-phenyl]-benzamide methanesulfonic acid is a white to slightly yellow powder. The main physico-chemical properties have been well described. It is freely soluble in water and sparingly soluble in methanol and practically insoluble in n-hexane. Imatinib is non-hygroscopic. Based on the literature survey imatinib exhibits polymorphism but the proposed manufacturer produces consistently a single crystalline form.

Manufacture

The active substance imatinib (as mesilate) is manufactured in 4 synthetic steps including using well-defined starting materials.

The structure elucidation of imatinib as mesilate was confirmed by Infrared, Ultra Violet, 1H NMR, 13C NMR and Mass spectroscopy. Experimental results of elemental analysis were comparable to theoretical values. XRD and DSC data showed that imatinib was consistently produced as a single polymorphic form.

The manufacturing process was critically evaluated as well as the carry-over of impurities, reagents, solvents and catalysts from the starting material into the final active substance.

Adequate in-process controls are applied during the synthesis. The specification and control methods for intermediate products, starting materials and reagents have been presented and were based on the appropriate studies

Specification

The specification of the active substance included tests for: description, solubility (Ph.Eur.), identification (IR, HPLC, XRD- Ph.Eur 2.2.24 and 2.2.37 and in-house methods) loss on drying (Ph.Eur 2.2.32), sulphated ash (Ph. Eur. 2.4.14), methanesulfonic acid content (potentiometric titration), heavy metals (Ph.Eur. 2.4.8), related substances (HPLC), assay (HPLC), residual solvents (GC), limits of sulphonate esters (GC), microbial limits (Ph.Eur. 2.6.12 and 2.6.13), particle size (laser diffraction).

The specification has been correctly discussed and the limits proposed for each test have been established taking into account the relevant ICH Guidelines (Q6A, Q3C (R3) and Q3A(R2)) and based on analytical data generated for imatinib mesilate batches. The limits were found to be acceptable from a safety point of view. The proposed specification is suitable to control the quality of the drug substance manufactured using the current process.

The analytical methods were described and the non-compendial methods validated in accordance with ICH guideline Q2 (R1). All parameters were correctly determined and comply with their acceptance criteria

Batch analysis data on three commercial- scale batches of imatinib mesilate are provided. The results are within specification and consistent from batch to batch.

For the primary packaging in contact with the active substance (polyethylene bags) IR spectrum and certificate of compliance have been provided as well as a description of the analytical methods.

Stability

Three commercial-scale batches kept in simulated commercial packaging (transparent PE bag in a polyethylene bag, further placed in a black polyethylene bag put into HDPE drum) were put under long

term (18 months at 25ºC/60%RH), intermediate (12 months at 30ºC/65%RH), and accelerated (3 months at 40ºC/75%RH) ICH conditions.

The parameters studied were: description, identification, loss on drying, related substances, Assay, Sulphonate esters and Microbial contamination. The parameters tested were considered stability indicating.

Stability results under long-term and intermediate conditions showed no significant degradation and confirmed the suitability of the analytical methods. Under accelerated conditions, some changes were observed with regard to polymorphism.

Stability studies were performed under forced conditions and degradation was observed under Acid, basic and Oxidation conditions.

The stability results support the proposed re-test period for the active substance stored in the proposed packaging materials.

2.2.3. Finished medicinal product

Pharmaceutical development

The aim of this product development was to formulate Imatinib 100 mg and 400 mg Film-coated Tablets which are robust, stable and bioequivalent to the reference product i.e. Glivec Tablets manufactured by Novartis Pharma GmbH.

Relevant physico-chemical characteristics such as solubility at different pH, density (impact on flow properties), particle size (affecting solubility and bioavailability), polymorphism (only one single crystalline form is produced), of the active substance were identified to optimise the product performance.

The excipients namely cellulose microcrystalline (diluent), crospovidone (disintegrant), hypromellose (binder), colloidal anhydrous silica (glidant), magnesium stearate (lubricant) used in this formulation are commonly used for solid oral dosage forms. All the excipients used are complying with the current version of Ph. Eur. except Opadry yellow (but each ingredient- hypromellose, talc, polyethylene glycol 8000, iron oxide red, iron oxide yellow complies with the Ph.Eur. or European directives).

A compatibility study between imatinib mesylate with different excipients was carried out and results indicate that the selected excipients were compatible with the active substance.

The primary aim of this development was to develop a stable formulation and to carry out the dissolution profile matching with the reference product.

The product development work was initiated with a composition similar to the qualitative composition of the reference product and the formulation was further improved to obtain a formulation with a similar dissolution profile. The pH solubility profile indicates that imatinib has sufficient solubility in pH range of 1.2 – 7.4 to achieve sink condition. The dissolution studies were carried out in in 0.01N HCl, pH 4.5 Acetate buffer and pH 6.8 Phosphate buffer. The discriminatory power of the dissolution method was confirmed. The dissolution profiles were found similar in the three media used.

A comparative bioequivalence study was performed between the test product Imatinib Mesylate Tablets 400 mg (Batch No.:PM0189) and Glivec 400 mg Tablets (Batch No. S0185). Imatinib Accord was found to be bioequivalent to the reference product Glivec. For further information please see the Clinical section of this report.

Comparative studies on impurities profiles showed that the impurity profile of Imatinib 100 mg & 400 mg Film-coated Tablets was found to be similar with the one from the reference product Glivec Tablets. No additional impurities could be observed in the test product.

The manufacturing process has been optimised by modifying the blending time, the lubrication time, the concentration of binder, lubricant and disintegrant. Studies were conducted on the common blend, the uncoated tablets, the coated tablets and coating solution, and satisfactory holding times and conditions were calculated before further processing.

The container closure system proposed is PVC/PVdC-Alu blisters, Alu- Alu blisters as described in the SmPC. There is also PPCP container intended to be used as a transportation pack. The packaging complies with the relevant EC directive 2002/72/EC and Ph. Eur. 3.1.11 and is adequate to support the stability and use of the Imatinib 100 mg and 400 mg film-coated tablets.

Adventitious agents

None of the ingredient used for Imatinib Accord was from animal or human origin and therefore no TSE risk could be foreseen. This is in line with the TSE CHMP guideline revision 3.

Manufacture of the product

The manufacturing process is well detailed and comprises of the main steps as follow: co-sifting of the ingredients, granulation, dry mixing and binding, drying, sizing (milling), blending, compression, film-coating and packaging.

The process is considered as a standard process and the formulation of Imatinib Film-coated Tablets 100 mg & 400 mg is quantitatively proportional. Both strengths are prepared from the same common granule.

Appropriate in-process controls of critical steps and intermediates (granules) have been conducted and include tests such as loss on drying and assay. In-process controls on tablets and during the packaging comprise tests such as appearance, average weight of tablets, hardness, and disintegration time, blister seal. The in-process controls were found adequate for this pharmaceutical form.

The process validation has been carried out on three consecutive batches of each strength of Imatinib Film coated Tablets 100 mg & 400 mg. The manufacturing process was found to be able to produce reproducibly a finished product of the intended quality.

Product specification

The finished product release and shelf-life specifications include the following tests: appearance (in-house), average weight (in-house), identification (in-house HPLC, TLC Ph.Eur 2.2.27 and colour identification of iron oxide), loss on drying (halogen moisture method), hardness (Ph.Eur. 2.9.8), dissolution (in-house), related substances (HPLC), uniformity of dosage unit (Ph.Eur. 2.9.40), assay (in-house HPLC), residual solvents (in-house GC), microbial quality (Ph.Eur. 2.6.12 and 2.6.13).

The specifications were adequately justified and considered suitable to control this type of oral solid dosage form. No safety concern could be foreseen with the related substances and residual solvents, the limits were in line with ICH guidelines.

All the analytical methods were described satisfactorily and non-compendial analytical methods were validated in accordance with ICH guidelines.

Three validation commercial–scale batches of Imatinib 100 mg & 400 mg Film-coated Tablets were manufactured at the proposed manufacturing site using imatinib active substance sourced from the

proposed active substance manufacturer. The results confirmed that the tablets can be manufactured consistently according to the finished product specification.

Stability of the product

Stability of three commercial-scale batches for each strength of Imatinib Accord 100 mg and 400 mg stored under ICH long term (up to 17 months at 25°C / 60% RH), intermediate (12 months at 30°C / 65% RH) and accelerated conditions (3 months at 40°C / 75% RH) were presented.

The batches were identical to those proposed for marketing and kept in the commercial packaging PVC/PVdC-Alu blisters, Alu-Alu blister (used for long term and accelerated conditions only) and/or PPCP (polypropylene co-polymer) container to be used as transportation pack.

Samples were tested for appearance, dissolution, loss on drying, assay, related substances and microbial contamination. The shelf life specification and test methods used were identical to those described in the control of the finished product. The tests methods were stability indicating.

During the accelerated studies, some results were found outside the specifications therefore intermediate studies were initiated. All results complied with the specifications and well within the acceptance criteria during the long-term and intermediate studies.

Additionally stability study was also carried out on PPCP container (transportation pack) under long term conditions up to 6 months at 25°C / 60% RH). Results were in compliance with the specification therefore coated tablets are to be repackaged in to blisters within 6 months from the date of bulk packing in to PPCP containers.

Based on available stability data, the proposed shelf-life and storage conditions as stated in the SmPC can be accepted.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of imatinib and Imatinib Accord 100 mg and 400 mg have been presented in a satisfactory manner. The results of tests carried out indicate satisfactory 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.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of Imatinib Accord 100 mg and 400 mg tablets is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physico-chemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and controlled in a satisfactory way.

2.2.6. Recommendation 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 Accord manufactured by Accord Healthcare Ltd. 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 film-coated tablets containing imatinib. 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 with the exception of the information related to the indications protected by market exclusivity at the time of the Marketing authorisation application.

No formal scientific advice by the CHMP was given for this medicinal product. For the clinical assessment Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1) in its current version is of particular relevance.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Exemption

A biowaiver for Imatinib Accord 100 mg was requested based on dissolution profiles. The two film-coated tablets strengths are manufactured with the same process and manufacturer. They have the same qualitative composition and proportional quantitative composition.

Dissolution tests have been performed for Imatinib 400 mg strength (bio-batch) and for 100 mg strength (three batches) at pH 1.2, 4.5 and 6.8 in paddle apparatus, 50 rpm, in 1000 mL of dissolution media. The values at 15 minutes are higher than 85% with the exception of Imatinib 400 mg (batch No.PM0189) at pH 6.8, Imatinib 100 mg (batch No. Pm0196) at pH 6.8 and Imatinib 100 mg (batch PM0242) at pHs 4.5 and 6.8, therefore f2 similarity factor has been calculated. The f2 values were within the acceptance values of 50-100 with the exception of Imatinib 400 mg vs. Imatinib 100 mg (batch PM0188). The same applies with the reference product. Therefore it was considered that Imatinib 400 mg and 100 mg have the same dissolution profile.

Clinical studies

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

Table 1. Tabular overview of clinical study

Types of study	Study identifies	Location of study report	Objective(s) of the study	Study design and type of control	Test product; Dosage regimen; Route of administration	Number of volunteers	Duration of treatment	Study status: Type of report
BE	Lambda 727-10	Module 5 (Part 1 to 7)	To characterize the pharmacokinetic profile of the test product relative to that of reference product in healthy, adult, human male subjects under fed conditions and to assess the bioequivalence. And to monitor the safety of the subjects.	An Open label, balanced, randomized, two-treatment, two-period, two-sequence, single dose, crossover, comparative oral bioequivalence study in healthy, adult, human, male subjects under fed conditions.	*Test Product:* Glivec® tablets 400 mg *Dosage regimen:* Single dose of 400 mg Tablets *Route of administration:* Oral	46 Volunteers	Single dose	Completed

2.4.2. Pharmacokinetics

Study 727-10

Methods

Study design

The study was an open label, balanced, randomised two-treatment, two-period, two-sequence, crossover, single oral dose, bioequivalence study of two formulations of imatinib tablets 400 mg in healthy, adult male subjects under fed conditions.

The treatment sequence is described in the table below.

	Period-I	Period-II
Sequence 1	Treatment-A (Test)	Treatment-B (Reference)
Sequence 2	Treatment-B (Reference)	Treatment-A (Test)

The subjects were administered the study drug in each period. The sequence of administration was determined by the randomisation schedule. Randomisation was generated after the finalisation of the protocol using SAS (version 9.2). A washout period of 11 days was considered sufficient between the successive dosing days.

Test and reference products

Test Product-A		
Formulation	:	Imatinib mesylate tablets 400mg
Manufactured by	:	Intas Pharma Ltd., India.
Batch No.	:	PM0189
Batch size	:	100000.00 nos
Manufacturing Date	:	07/ 2011
Expiry Date	:	06/ 2013
Storage Condition	:	Do not store above 30°C, Protect from moisture.
Reference Product-B		
Formulation	:	Glivec® Tablets [Imatinib mesylate tablets 400mg]
Mfg. by	:	Novatris Pharma GmbH, Nuremberg, Alemania
MAH	:	Novartis Europharm Limited, West Sussex, UK.
Lot No.	:	S0185
Expiry Date	:	12/2012
Storage Condition	:	Do not store above 30°C, Protect from moisture.

Population(s) studied

As per the protocol, 44 subjects were dosed in Period-I of the trial and all the dosed 44 subjects completed the clinical phase of the study successfully. Subjects were non-smoker, healthy, adult, male volunteers between 18 to 45 years of age (both inclusive), having a BMI between 18.5 to 30.0 kg/m2 (both inclusive).

Analytical methods

The plasma samples of subjects were analysed using a validated LC-MS/MS method for imatinib at the bioanalytical facility of Lambda Therapeutic Research Ltd. The method validation report was provided

by the Applicant. Calibration curves using a 9-point calibration curve standards for imatinib, with concentrations ranging from 5.022 ng/mL to 3515.861 ng/mL, were used to determine the concentrations of imatinib in the samples of various subjects.

Pharmacokinetic variables

Efficacy of the formulations, based on the following primary and secondary pharmacokinetic parameters were assessed.

Primary efficacy variables

- Maximum measured plasma concentration (Cmax)
- Area under the plasma concentration-time curve from concentration at 0h to the time of last measurable concentration (AUC0-l)
- Area under the plasma concentration-time curve from concentration at 0h to infinity (AUC0-∞)

Secondary efficacy variables

- Time-point of maximum measured plasma concentration (Tmax)
- Elimination rate constant (λz)
- Half-life of drug elimination during the terminal phase (t1/2)
- Residual Area (AUC_%Extrap_obs)

These parameters were derived individually for each analysed subject from the concentration vs. time profiles of imatinib in plasma. Actual time-points were used for all the samples collected.

The pharmacokinetic parameters were calculated by non-compartmental model using WinNonlin Professional Software Version 5.3 (Pharsight Corporation, USA).

Statistical methods

Dataset for the estimation of pharmacokinetic parameters was prepared using WinNonlin Professional Software (Version 5.3) for imatinib.

Descriptive statistics was computed and reported for all pharmacokinetic parameters of imatinib.

The comparison of the pharmacokinetic parameters was carried out using PROC GLM of SAS Version 9.2 (SAS Institute Inc., USA). The same program was used to carry out the analysis of variance for un-transformed and ln-transformed pharmacokinetic parameters Cmax, AUC0-l and AUC0-∞ for imatinib.

ANOVA model included Sequence, Formulation and Period as fixed effects.

An F-test was performed to determine the statistical significance of the effects involved in the model at a significance level of 5% (alpha=0.05).

Two one sided test for bioequivalence and 90 % confidence interval for both the un-transformed and ln-transformed ratios of the least squares means between the formulations were calculated for imatinib.

Criteria for conclusion of bioequivalence were as follows:

Bioequivalence of Test Product-A vs. Reference Product-B was concluded if the 90 % confidence interval fell within the acceptance range as defined below for ln-transformed pharmacokinetic parameters Cmax, AUC0-l and AUC0-∞ for imatinib.

Parameters	Range of Ln-transformed 90% CI
C_{max}, AUC_{0-t} and $AUC_{0-\infty}$	80.00-125.00%

Results

Table 2. Descriptive statistics of Formulation means for imatinib (n=44)

Parameters (Units)	Mean ± SD (Un-transformed data)	
	Test Product-A	Reference Product-B
T_{max} (h)*	4.500	4.500
C_{max} (ng / mL)	1985.953 ± 613.6962	2070.029 ± 628.5314
AUC_{0-t} (ng.h / mL)	37993.818 ± 11716.6372	38764.743 ± 11560.7044
$AUC_{0-\infty}$ (ng.h / mL)	40114.168 ± 12511.3078	40691.198 ± 12332.6081
λ_z (1 / h)	0.046 ± 0.0090	0.046 ± 0.0086
$t_{½}$ (h)	15.708 ± 3.3197	15.565 ± 2.8786
AUC_% Extrap_Obs (%)	5.094 ± 4.0768	4.521 ± 3.0132

Table 3. Geometric least squares mean, ratios and 90 % confidence interval for imatinib (n= 44)

Parameters (Units)	Ln-transformed data			90% Confidence Interval (Parametric)
	Geometric Least Squares Mean			
	Test Product-A	Reference Product-B	Ratio (A / B)%	
C_{max} (ng / mL)	1895.884	1977.262	95.9	90.94-101.09%
AUC_{0-t} (ng.h / mL)	36264.413	37070.409	97.8	93.22-102.66%
$AUC_{0-\infty}$ (ng.h / mL)	38248.206	38845.726	98.5	93.79-103.37%

Based on the submitted bioequivalence study, the test product is equivalent to the reference with respect to the extent and rate of absorption / exposure. The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} of imatinib were inside the normal range of acceptability (0.80 – 1.25).

Safety data

Four adverse events (AEs) (1 case of upper respiratory tract infection, 1 case of urinary tract infection, 1 case of diarrhoea and 1 case of increased total white blood cell) were reported by 4 subjects during the conduct of the study. Three AEs were reported in Period-I and one AE in the post-study. Three AEs were reported after the receipt of Reference Product-B and one adverse event was reported after the receipt of Test Product-A. All the 4 AEs were mild in nature and were followed-up until resolution.

Conclusions

Based on the presented bioequivalence study Imatinib Accord 400 mg film-coated tablets, is considered bioequivalent with the Reference Product Glivec 400 mg film-coated tablets.

The results of study 727-10 with 400 mg formulation can be extrapolated to other strengths 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

Based on the submitted bioequivalence study, Imatinib 400 mg film-coated tablets, Intas Pharma Ltd, when compared with the Reference Product Glivec 400 mg film-coated tablets, Novartis Europharm Ltd., meet the bioequivalence criteria with respect to the rate and extent of absorption of imatinib mesilate as set in the Protocol.

2.4.6. Conclusions on clinical aspects

The CHMP considers Imatinib Accord 100 mg and 400 mg film-coated tablets 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 did not require the applicant to submit a risk management plan since the application concerns a medicinal product containing a known active substance for which no safety concern requiring additional risk minimisation activities has been identified.

The CHMP, having considered the data submitted, was of the opinion that routine pharmacovigilance was adequate to monitor the safety of the product.

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 film-coated tablets. The reference product is Glivec

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 an open label, balanced, randomised, two-treatment, two-period, two-sequence, crossover, single oral dose, bioequivalence study of two formulations of imatinib tablets 400 mg in healthy, adult male subjects under fed conditions. 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 Accord 400 mg film-coated tablets met the protocol-defined criteria for bioequivalence when compared with Glivec 400 mg film-coated tablets. The point estimates and their 90% confidence intervals for the parameters AUC0-t,, AUC0-□, and Cmax 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.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus decision that the benefit-risk balance of Imatinib Accord 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 product 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)**

Not applicable.