18 October 2012
EMA/CHMP/593709/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Imatinib Teva

International non-proprietary name: **imatinib**

Procedure No. **EMEA/H/C/002585**

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Product information

Marketing authorisation application

Name of the medicinal product:	Imatinib Teva
Applicant:	Teva Pharma B.V. Computerweg 10 NL-3542 DR Utrecht The Netherlands
Active substance:	imatinib mesilate
International Nonproprietary Name:	imatinib
Pharmaco-therapeutic group (ATC Code):	Protein kinase inhibitors (L01XE01)
Therapeutic indication(s):	treatment of Philadelphia chromosome (bcr-abl) positive (Ph+) chronic myeloid leukaemia (CML)
Pharmaceutical form(s):	Film-coated tablet and hard capsules
Strength(s):	100 mg, 400 mg
Route(s) of administration:	Oral use
Packaging:	blister (OPA/AL/PVC/AL), blister (PVC/PE/PVdC/PE/PVC/AL)
Package size(s):	120 capsules, 120 tablets, 120 x 1 capsule, 120 x 1 tablet, 180 x 1 capsule, 180 x 1 tablet, 20 x 1 capsule, 20 x 1 tablet, 30 capsules, 30 tablets, 30 x 1 capsule, 30 x 1 tablet, 60 capsules, 60 tablets, 60 x 1 capsule, 60 x 1 tablet, 90 capsules, 90 tablets, 90 x 1 capsule, 90 x 1 tablet

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ABBREVIATIONS

AGP	alpha-1 acid glycoprotein
ALL	acute lymphoblastic leukaemia
ANOVA	analysis of variance
AUC	area under the curve
CEL	chronic eosinophilic leukaemia
CML	chronic myeloid leukaemia
DFSP	dermatofibrosarcoma protuberans
EMA	European Medicines Agency
GIST	Gastrointestinal stromal tumour
HES	hypereosinophilic syndrome
ICH	International Conference on Harmonization
MDS/MPD	myelodysplastic syndrome/myeloproliferative diseases
mg	milligrams
mg/m2	milligrams/square meter
PDGF	platelet-derived growth factor
PDGFR	platelet-derived growth factor receptor
Ph	Philadelphia chromosome

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Teva Pharma B.V. submitted on 15 November 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Imatinib Teva, 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 19 May 2011. 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 indication treatment of Philadelphia chromosome (bcr-abl) positive (Ph+) chronic myeloid leukaemia (CML).

The legal basis for this application refers to:

Article 10(1) of Directive 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

The market exclusivity of the chosen reference product expired on 12 November 2011 for the condition chronic myeloid leukaemia.

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 hard capsules
- Marketing authorisation holder: Novartis Europharm Limited
- Date of authorisation: 07-11-2001
- Marketing authorisation granted by:
  - Community
  - Community Marketing authorisation number: EU/1/01/198/002 - EU/1/01/198/006

■ 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
- Marketing authorisation holder: Novartis Europharm Limited

- Date of authorisation: 07-11-2001
- Marketing authorisation granted by:
  - Community
  - Community Marketing authorisation number: EU/1/01/198/002 - EU/1/01/198/006

■ 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: 11-11-2003
- Marketing authorisation granted by:
  - Community
  - Community Marketing authorisation numbers: EU/1/01/198/009, EU/1/01/198/010 and EU/1/01/198/013

Scientific advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

The product has been authorised in Croatia.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Arantxa Sancho-Lopez

- The application was received by the EMA on 15 November 2011.
- The procedure started on 21 December 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 09 March 2012.
- During the meeting on 16-19 April 2012, 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 20 April 2012.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 20 July 2012.
- The Rapporteur circulated the Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 03 September 2012.
- During the CHMP meeting on 17-20 September 2012, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 20 September 2012.
- The Rapporteur circulated the Assessment Report on the applicant’s responses to the List of Outstanding Issues to all CHMP members on 04 October 2012.

- During the meeting on 15-18 October 2012, 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 Imatinib Teva on 18 October 2012.
- CHMP adopted a report on similarity of Imatinib Teva with Tasigna and Sprycel on 19 April 2012.

2. Scientific discussion

2.1. Introduction

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

The active substance of Imatinib Teva 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 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.

Bioequivalence to the reference product was demonstrated by two bioequivalence studies at single dose under fed conditions. The studies were performed in healthy volunteers. One study was performed with the 400 mg strength film coated tablets and the second with the 400 mg capsules.

The approved indication is:
Imatinib Teva 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.
- Adult patients with Ph+ CML in blast crisis.

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.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film coated tables and hard capsules containing 100 mg and 400 mg of imatinib as active substance. The composition is described in section 6.1 of the SmPC.

The product is available in blisters as described in section 6.5 of the SmPC.

2.2.2. Active substance

The active substance is a white to off white or slightly yellowish crystalline powder, slightly hygroscopic, freely soluble in water, soluble in methanol and slightly soluble in ethanol.

The chemical name is 4-[(4-Methyl-1-piperazinyl) methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl] aminophenyl]benzamide methanesulfonate salt.

Imatinib mesylate has no chiral center hence no chirality. Polymorphism has been observed for imatinib mesylate. However, there is no impact on the quality and performance of drug product since the polymorphs of imatinib mesylate are highly soluble.

The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure within the current Marketing Authorisation Application.

Manufacture

Imatinib mesylate is manufactured by different manufacturers and the Active Substance Master File (ASMF) procedure was followed for all manufacturers. The route of synthesis differs for the sites. The route of synthesis was briefly described in the open part but the detailed information was provided in the restricted part of the ASMF. The process was acceptably described for all manufacturing sites.

Imatinib mesylate is synthesized in three main steps using commercially available starting materials.

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

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

Specification

The active substance specification includes tests for appearance (visual inspection), identity (IR, HPLC, XRPD), assay (HPLC), impurities (HPLC), residual solvents (GC), water content (KF), sulphated ash (Ph Eur) and heavy metals (Ph Eur). Additional specifications have been set for methanesulphonic acid content (potentiometric titration).

Impurities have been evaluated and found to be acceptable from the point of view of safety.

The analytical methods are essentially the same in the different manufacturing sites and are suitable to control the quality of the active substance. The methods have been well described and validated according to ICH Q2 (R1).

Batch analysis data (3 commercial scale batches) of the active substance are provided. The results comply with the specifications and therefore confirm consistency and uniformity of the manufacturing processes.

Stability

Three production scale batches of the active substance packed in the intended commercial package were placed on stability testing as per ICH conditions: under long term (25°C/60%RH) for up 48 months, and accelerated (40°C/75%RH) for up six months conditions. Photostability test following ICH guidelines Q1B was performed on one batch. Results on stress conditions, i.e., heat treatment, acid treatment, base treatment, oxidizing agent treatment and water treatment were also provided.

The parameters tested are the same as for release.

The stability results indicate that the drug substance manufactured by the proposed suppliers is sufficiently stable. The stability results support the proposed retest period.

2.2.3. Finished medicinal product

Pharmaceutical development

The proposed medicinal product is film-coated tablets and hard capsules, available in two strengths, 100mg and 400 mg. Imatinib Teva film-coated tablets 100 mg are dark yellow to brownish orange round film coated tablets debossed with IT and 1, divided by score line on one side. Imatinib film-coated tablets 400 mg are dark yellow to brownish orange oblong film coated tablets debossed with IT and 4, divided by score line on one side. Imatinib capsules 100 mg are non transparent orange capsules with black marking 7629 on the capsule body and black marking TEVA on the capsule cap. Imatinib capsules 400 mg are non transparent orange capsules with black marking 7630 on the capsule body and black marking TEVA on the capsule cap.

Imatinib film-coated tablets 100 mg and 400 mg and Imatinib capsules 100 mg 400 mg are packed into two types of packaging systems, i.e., OPA/Al/PVC//Al blisters and PVC/PE/PVdC/PE/PVC//Al blisters.

Imatinib film-coated tablets

The formulation of Imatinib film-coated tablets was designed to obtain a dosage form similar to the reference product, Glivec 400 mg film-coated tablets.

Imatinib film coated tablets are immediate release oral solid dosage form, containing imatinib mesylate as the active ingredient.

Excipients used in the formulation are well known and widely used for this dosage form. The excipients used include: anhydrous dibasic calcium phosphate, crospovidone, water, magnesium stearate and Opadry as coating coating agent.

Bioequivalence has been established between the 400 mg strength batches with batches of the reference product.

Additionally, comparative *in vitro* dissolution profiles of the test products (including additional strength not tested for bioequivalence) and the reference product were provided to support the essential similar character.

Dissolution profiles of Imatinib film coated tablets 400 mg manufactured using all sources of the drug substance, as well as Imatinib film coated tablets 100 mg was shown to be similar.

In vitro dissolution studies were conducted in different media and met the F_2 requirements.

Investigation on polymorphism during stability studies confirmed that storage of tablets did not lead to any relevant changes in solid state characteristics. In addition, it was also confirmed that polymorphic form has been preserved after production.

The test of subdivision of tablets has been performed according to Ph. Eur. All results comply with the pharmacopoeial requirements.

Imatinib capsules

The formulation development phase was conducted to obtain a formulation that would use standard technology, standard excipients and would have a rapid drug release similar to the reference product.

Excipients used in the formulation are well known and widely used for this dosage form. The excipients used include: mannitol, crospovidone, silica colloidal anhydrous, magnesium stearate. Excipients used for the capsule shell include: gelatin, titanium dioxide, yellow ferric oxide and red ferric oxide.

Appropriate excipients in optimal quantity in the formulation were selected in order to match the dissolution profiles of drug reference product. Pre-formulation studies were performed to test and determine compatibility of the proposed excipients with the active substance. The manufacturing process was developed in order to deliver a final product of satisfying stability. The scale up of the process was done by defining optimal process parameters and ranges.

Bioequivalence study was performed with the 400 mg strength showing bioequivalence to the reference product, Glivec 400 mg film-coated tablets.

Dissolution studies were performed in order to demonstrate *in vitro* equivalence between the reference product and imatinib capsules with regard to imatinib release from the product. The discriminatory nature of the method was evaluated. In all tested dissolution media the results show a fast and complete dissolution (> 85% in 15 minutes).

The additional strength of the product series, 100mg, has not been tested *in vivo* for bioequivalence. Exemption of a bioavailability study for the 100 mg strength was acceptable since all requirements of a biowaiver for this strength have been fulfilled.

The primary packaging proposed is described as stated in the SmPC. The material complies with PhEur requirements, and it is adequate to support the stability and use of the product.

Adventitious agents

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

Manufacture of the product

Imatinib film-coated tablets 100 mg and 400 mg

The manufacturing process consists of five main steps: (1) granulation, (2) homogenisation of the granules, (3) compression, (4) film coating and (5) packaging. The manufacturing process is considered to be a standard manufacturing process for film-coated tablets. The manufacturing process has been validated by a number of studies for the major steps of the manufacturing process and has been demonstrated to be capable and to be able to reproducibly produce finished product of the intended quality. The in process controls are adequate for this tablet preparation. The manufacturing process has been satisfactorily validated at full scale on three batches per strength.

Imatinib capsules 100 mg and 400 mg

The manufacturing process consists of seven main steps: (1) mixing, (2) roller compaction, (3) screening, (4) milling, (5) homogenisation, (6) encapsulation and (7) packaging. The process is considered to be a standard manufacturing process for capsules.

The manufacturing processes have been adequately described and the critical steps have been identified. Adequate flow-charts were provided and the different steps of the manufacturing processes are described, together with equipment type and operating parameters.

The validation protocol proposed for the full scale batches for the capsule formulation has been provided and the quality of the production batches will be evaluated through the results of in process testing as well as the results of finished product testing.

Product specification

The finished product release specifications include appropriate tests for visual description, identification (HPLC and UV), assay (HPLC), uniformity of dosage unit (PhEur), related substances (HPLC), subdivision of tablets (PhEur), dissolution (PhEur), loss on drying (PhEur), identification of colorants and microbiological quality (PhEur). Analytical methods have been well described and validated.

The proposed limits for the impurities are in accordance with the ICHQ3B guideline.

Batch analysis results on three commercial batches per strength and per pharmaceutical form confirm consistency and uniformity of manufacture and indicate that the process is capable and under control.

Stability of the product

Imatinib film-coated tablets 100 mg and 400 mg

Stability data of 9 full scale batches of 100 mg and 6 full scale batches of 400 mg film coated tablets stored under long term conditions for 24 months at 25ºC/60%RH, and for up to six months under accelerate conditions at 40ºC/75%RH according to ICH guidelines were provided. The batches of imatinib film coated tablets are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for assay, related substances, dissolution, loss on drying, description and microbial limits. The analytical procedures used were stability indicating.

In addition, freezing testing has been performed. Freezing testing has shown that the product is not sensitive to freezing.

Imatinib capsules 100 mg and 400 mg

Stability data of 6 full scale batches of 100 mg and 6 full scale batches of 400 mg batches of imatinib capsules stored under long term conditions for 12 months at 25ºC/60%RH, and for up to six months under accelerate conditions at 40ºC/75%RH according to ICH guidelines were provided. The batches of imatinib capsules are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for assay, related substances, dissolution, water content, description and microbial limits. The analytical procedures used were stability indicating.

Freezing and photostability testing results have shown that the product is not sensitive to freezing or to light.

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.

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 Teva manufactured by Teva 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 new ERA studies is acceptable.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for film-coated tablets and hard capsules containing imatinib. 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 waiver of two proportional strengths has been applied for based on dissolution profiles. The different film-coated tablets and hard capsules strengths are manufactured with the same process by the same manufacturer. They have the same qualitative composition and a proportional quantitative composition. The evidence submitted to show that *in vitro* dissolution profiles are similar is enough in the assessor's opinion to grant a biowaiver for the proportional formulation of lower strength since the necessary information has been provided.

Based on the submitted bioequivalence studies, study 1 (film-coated tablets) and study 2 (hard capsules), both met the bioequivalence criteria with respect to the rate and extent of absorption of Imatinib as set in the Protocol.

Clinical studies

To support the marketing authorisation application the applicant conducted two bioequivalence study under fed conditions. Both BE studies were a Single-Dose Randomized, Open-Label, Two-Way Crossover, Comparative Bioavailability Study in Normal, Healthy Subjects under Fed Conditions.

Table 1. Tabular overview of clinical studies

Study type	Study	Objective(s) of the study	Study Design and Type of control	Test product(s); Dosage regimen; Route of administration	Number / type of subjects	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; type of report
BE	Study 1	To evaluate and compare the relative Bioavailability and therefore the bioequivalence of two different formulations of imatinib after a single oral dose administration under fed conditions.; Monitor the safety	Single center, randomized, single dose, laboratory-blinded, 2-period, 2-sequence, crossover study. Fed state	Test: Imatinib 400mg tablets; Reference: 400 mg film-coated tablets, Novartis Germany; 1x400 mg, oral	42 (41 completed the study and were included in PK statistical analyses)	Healthy male subjects	Single dose	Complete, full
BE	Study 2	Compare the pharmacokinetic profiles of Imatinib mesylate capsules versus tablets; Monitor the safety	Open label, randomized, 2-way crossover study. Fed state	Test: Imatinib mesylate capsules 400mg; Reference: 400 mg film-coated tablets, Novartis Germany; 1x400 mg, oral	20 (20 completed the study and were included in PK statistical analyses)	Healthy male and/or post-menopausal/surgically sterile female subjects	Single dose	Complete, abbreviated

2.4.2. Pharmacokinetics

Methods

Study design

Study 1 - Film-coated tablets

The study is a single centre, randomized, single dose, laboratory-blinded, 2-period, 2-sequence, crossover design in healthy male subjects, Comparative Bioavailability Study Imatinib 400 mg film-coated tablet and Glivec 400 mg film-coated tablet (Novartis Pharma GmbH, Germany) under Fed Conditions.

Study 2 - Hard capsules

The study is an open-label, single-dose, randomized, two-period, two-sequence, two-treatment, crossover study, designed to evaluate the comparative bioavailability of a formulation of Imatinib 400 mg capsules to Glivec 400 mg film-coated tablets (Novartis Pharma GmbH, Germany) to healthy male and female subjects under fed conditions

Test and reference products

Study 1 - Film-coated tablets

Test Product: Imatinib Teva 400 mg film coated tablets.

Reference Product: Glivec 400 mg film coated tablets, manufactured by Novartis Pharma GmbH, Germany (marketed in Germany). Batch number: S0104. Expiry date: July 2011. Assay (content): 97.8% of label claim.

Study 2 - Hard capsules

Test Product: Imatinib Teva 400 mg hard capsules.

Reference Product: Glivec 400 mg film coated tablets, manufactured by Novartis Pharma GmbH, Germany (marketed in Germany). Batch number: S0157. Expiry date: June 2012. Assay (content): 99.6% of label claim.

Population(s) studied

Study 1 - Film-coated tablets

Of the forty-two (42) healthy male subjects who were included in the study, forty-one (41) subjects completed the crossover design and received a single oral dose of the assigned formulation on day 1 and day 15.

Subject # 037 withdrew consent before dosing of period 2 due to an adverse event (toothache of severe intensity) and received only one single oral dose of the Glivec® 400 mg Film-Coated Tablet. Samples collected in period 1 for this subject were analyzed but excluded from the statistical analysis.

Forty-two (42) subjects were analyzed and forty-one (41) were included in the pharmacokinetic and statistical analysis (Subjects # 001-036 and 038-042).

Study 2 - Hard capsules

Of the twenty (20) healthy male and female subjects who were included in the study, twenty (20) subjects completed the crossover design and received a single oral dose of the assigned formulation on

day 1 and day 15. All subjects were analyzed and were included in the pharmacokinetic and statistical analysis (Subjects # 01-020).

Analytical methods

Study 1 - Film-coated tablets

Pre-study validation

The analytical method validation report describes the method validation carried out for the determination of Imatinib and N-Desmethyl Imatinib in human plasma using K2EDTA as anticoagulant. The compounds were identified and quantified using reverse-phase HPLC with MS/MS detection over a theoretical concentration range of 10.0 ng/mL to 4000.0 ng/mL for Imatinib and 5.00 ng/mL to 400.00 ng/mL for N-Desmethyl Imatinib.

The analytes have no chiral centers and therefore no enantiomers for these compounds exist.

The concomitant medications were tested and met SOP acceptance criteria as all samples were free of interference.

In-study validation

Bioanalitycal report describes the analysis of Imatinib in human K2EDTA plasma over the concentration range of 10.0 ng/mL to 4000.0 ng/mL (Weighting Factor 1/c) using Imatinib-d8 as IS

The in-study validation shows an acceptable calibration standards (In all runs, there were 5 calibrations standards out of the acceptance range and only 2 standards were rejected in the calibration curve) and QC values.

The reasons for reanalysis of samples are acceptable for unacceptable internal standard response.

Dilution samples were not necessary.

The study samples were analysed, with a calibration curve, and four sets of non-zero QCs in duplicate (8 QCs). Since study samples from three subjects (120 samples) were analysed in each run, the number of QCs samples relative to the number of study samples is adequate.

Incurred Sample Reproducibility was acceptable.

The mainly samples reintegration correspond to Period 1 and 2; hour 1.0. and it was not carried out for subject No. 010 and 018 with C_{max} at 1.0. As, Imatinib C_{max} achieved within 2-4 hours post-dose the samples reintegration is acceptable. The chromatogram integration SOP LAP-1015-05 was submitted.

The long term stability data in frozen human plasma stored at -20 ºC was 44 days to cover the 35 days maximum storage samples at -20 ºC

Study 1 - Hard capsules

Pre-study validation

The analytes have no chiral centers and therefore no enantiomers for these compounds exist.

The analytical method validation report describes the method for the determination of Imatinib in human plasma using K2EDTA as anticoagulant. This validation report provides the results pertaining to selectivity, matrix effect, hemolyzed and lipemic plasma experiments, specificity (concomitant medication and hormonal contraceptives interference), injection carryover, recovery, within and between batch precision and accuracy, dilution integrity, linearity, evaluation of Imatinib in presence of Desmethyl Imatinib and stability. The compounds were identified and quantified using reverse-phase

HPLC with MS/MS detection over a theoretical concentration range of 10.0 ng/mL to 5000.0 ng/mL for Imatinib.

A quadratic equation was used to evaluate Imatinib standard concentrations. All calibration points are weighted by a defined factor.The concomitant medications were tested and met SOP acceptance criteria as all samples were free of interference.

In-study validation

Bioanalitycal report describes the analysis of Imatinib in human K2EDTA plasma over the concentration range of 10.0 ng/mL to 5000.0 ng/mL (weighting factor 1/x) using Imatinib-d4 as IS.

The in-study validation shows an acceptable calibration standards and QC values. All calibrations standards and QCs were within acceptance range.

The study samples were analysed, with a calibration curve, and four sets of non-zero QCs in quadruplicate (16 QCs). Since study samples from four subjects (184 samples) were analysed in each run, the number of QCs samples relative to the number of study samples is adequate.

The reasons for reanalysis of samples are acceptable for unacceptable internal standard response and extraction error.

Dilution samples were not necessary.

Incurred Sample Reproducibility was acceptable.

The long term stability data in frozen human plasma stored at -25 ºC ± 10 ºC was 1008 days to cover the 24 days maximum storage samples at -25 ºC ± 10 ºC.

Pharmacokinetic variables

For both studies, the main pharmacokinetic parameters of interest for this study will be C_{max} and AUC0-72. Other parameters such as Tmax, AUC∞, AUC0-72/∞, Kel and T½el were provided for information purposes only. The natural logarithmic transformation of C_{max}, AUC0-72 and AUC∞ was used for all statistical inference. The pharmacokinetic analysis was performed using Kinetic Version 9.01.

The main absorption and disposition parameters were estimated using a non-compartmental approach with a log-linear terminal phase assumption. The trapezoidal rule was used to estimate the area under the curve and the terminal phase were estimated by maximizing the coefficient of determination estimated from the log-linear regression model. However, they were not estimated for individual concentration-time profiles where the terminal log-linear phase cannot be reliably characterized.

Statistical methods

For both studies, the statistical analysis was applied to quality assured data from all subjects in the final dataset, with unbalanced groups if necessary. The PROC GLM procedure from SAS® was used. Concentration-time profiles where subjects exhibit pre-dose levels higher than 5% of the corresponding C_{max} would be excluded from the statistical analysis. Concentration-time profiles where subjects exhibit non-zero predose levels equal to or less than 5% of the corresponding C_{max} will be included in the statistical analysis without baseline correction.

Analysis of variance (ANOVA) was applied to log-transformed AUCt and C_{max} parameters. The significance of the sequence, period, treatment, and subject-within-sequence effects was tested.

Using the same statistical model, the least-squares-means, the differences between the treatments least-squares-means, and the corresponding standard errors of these differences was estimated for log-transformed AUCt and C_{max} parameters. Based on these statistics, the ratios of the geometric means for treatments and the corresponding 90% confidence intervals were calculated.

Based on the log-transformed parameters, the following criteria were used to evaluate the bioequivalence between the test and reference products:

The 90% confidence intervals of the relative mean AUCt and C_{max} of the test to reference products should be between 80.00% and 125.00%.

Results

Study 1 - Film-coated tablets

Based on the statistical analysis submitted by the Applicant both test products are equivalent to the reference with respect to the extent and rate of absorption / exposure. The 90% confidence intervals calculated for AUC(0-72) and C_{max} of Imatinib were inside the normal range of acceptability (0.80–1.25). Also the 90% CI for $AUC_{(0\text{-}inf)}$ was calculated and were also inside the normal range (0.80-1.25).

Study 2 - Hard capsules

Based on the statistical analysis submitted by the Applicant both test products are equivalent to the reference with respect to the extent and rate of absorption/exposure. The 90% confidence intervals calculated for $AUC_{(0\text{-}72)}$ and C_{max} of Imatinib were inside the normal range of acceptability (80.0 – 125.0).

Safety data

The safety profile of both products seems to be comparable although it is obvious that the design was not powered to compare the safety profile. No difference in the safety profile can be anticipated.

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 and conclusion on clinical aspects

Based on the submitted bioequivalence studies, for Study 1 - film-coated tablets and for Study 2 - hard capsules, both meet the bioequivalence criteria with respect to the rate and extent of absorption of Imatinib as set in the Protocol Imatinib Teva is considered bioequivalent with Glivec.

The results of Study 1 - film-coated tablets and Study 2 - hard capsules with the 400 mg formulation can be extrapolated to the 100 mg strengths (film-coated and hard capsules) as the Applicant performed comparative dissolution profiles in paddle for film-coated tablets and in basket for hard capsules and new dissolution profiles shown to be similar, according to conditions in Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98, section 4.2.

2.5. Pharmacovigilance

Detailed description of the pharmacovigilance system

The applicant has provided documents that set out a detailed description of the system of pharmacovigilance (DDPSv10, dated on February 2011). A statement signed by the applicant and the qualified person for pharmacovigilance, indicating that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country has been provided.

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.

Additionally data regarding use during pregnancy; tolerability during pregnancy and pregnancy outcomes (if applicable/available), should be specifically registered and discussed in the PSUR.

PSUR submission

Not applicable.

User consultation

The methodology of the user consultation survey is considered satisfactory and the results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

This package leaflet was found to contain all the necessary information in a way that is accessible and understandable to those who participated in this test.

3. Benefit-risk balance

This application concerns a generic version of imatinib film-coated tablets and hard capsules. 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 studies form the pivotal basis with a single centre, randomized, single dose, laboratory-blinded, 2-period, 2-sequence, crossover design for the film-coated tablets bioequivalence study and an open-label, single-dose, randomized, two-period, two-sequence, two-treatment,

crossover design for the hard capsules bioequivalence study. The studies 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 Teva met the protocol-defined criteria for bioequivalence when compared with 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.

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

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Imatinib Teva is not similar to Tasigna and Sprycel 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 Teva in 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.

is favourable.

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.

The CHMP 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

Pharmacovigilance System

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

Risk management system

Not applicable.

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

Not applicable.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the member states.

Not applicable.