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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Imatinib Actavis

International non-proprietary name: Imatinib

Procedure No. EMEA/H/C/002594

Assessment report as adopted by the CHMP with all commercially confidential information deleted

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List of abbreviations

AEs	adverse events
ALL	acute lymphoblastic leukaemia
Al or Alu	Aluminium
ASMF	active substance master file
AUC0-t	Area under the plasma concentration curve from administration to last observed concentration at time t.
AUC0-∞	Area under the plasma concentration curve extrapolated to infinite time
BE	Bioequivalence
BMI	body mass index
Cmax	Maximum plasma concentration
CML	chronic myeloid leukaemia
CLcr	creatinine clearance
CHMP or CPMP	Committee for Medicinal Products for Human Use
EMA	European Medicines Agency
EP or Ph. Eur.	European Pharmacopoeia
HPLC	high pressure liquid chromatography
GC	gas chromatography
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
ICH	International Conference on Harmonisation
IPC	in-process controls
IR	infra-red
Kel	elimination constant
MAH	Marketing Authorisation Holder
Ph+	Philadelphia chromosome (bcr-abl) positive
PK	pharmacokinetics
PSUR	periodic safety update report
PVC	Polyvynilchloride
RH	relative humidity
RMP	Risk Management Plan
SAEs	serious adverse events
SmPC or SPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
TIH	tumour-induced hypercalcaemia
tmax	Time until Cmax is reached
TSE	transmissible spongiform encephalopathy
UV	ultra violet
XRD	X-ray diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Actavis Group PTC ehf. submitted on 1 December 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Imatinib Actavis, 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 23 June 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:

Imatinib Actavis 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.

The legal basis for this application refers to:

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

The application submitted is composed of administrative information, complete quality data and bioequivalence studies with the reference medicinal product Glivec instead of non-clinical and clinical 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: Glivec

■ 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 50 mg & 100 mg Hard Capsules, 100 mg & 400 mg Film-coated tablets
- Marketing authorisation holder: Novartis Europharm Ltd.
- Date of authorisation: 07/11/2001
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/01/198/001-006, EU/1/01/198/007-013

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

- Product name, strength, pharmaceutical form: Glivec 50 mg & 100 mg Hard Capsules, 100 mg & 400 mg Film-coated tablets
- Marketing authorisation holder: Novartis Europharm Ltd.
- Date of authorisation: 07/11/2001
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/01/198/001-006, EU/1/01/198/007-013

■ 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 100 mg Hard Capsules, 100mg and 400 mg Film-coated tablets
- Marketing authorisation holder: Novartis Europharm Ltd.
- Date of authorisation: 07/11/2001
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number(s): EU/1/01/198/005, EU/1/01/198/008, EU/1/01/198/010

Scientific advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

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

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was Reynir Arngrímsson

- The application was received by the EMA on 1 December 2011.
- The procedure started on 21 December 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 9 March 2012.
- During the meeting 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 19 April 2012.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 11 October 2012.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 22 November 2012.
- During the CHMP meeting 10-13 December 2012, the CHMP agreed on a list of outstanding issues to be addressed in an oral explanation or in writing by the applicant. The final consolidated List of Questions was sent to the applicant on 13 December 2012.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 18 January 2013.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 05 February 2013.
- During the meeting on 18-21 February 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 Actavis.
- The CHMP adopted the reports on similarity of Imatinib Actavis with Tasigna and Sprycel on 19 April 2012 and updated 21 February 2013.

2. Scientific discussion

2.1. Introduction

Imatinib Actavis 50 mg and 100 mg capsules and 100 mg and 400 mg film-coated tablet is a generic medicinal product of Glivec, which has been authorised in the EU since 7 November 2001.

The active substance of Imatinib Actavis 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 (Ph+) chronic myeloid leukaemia (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.

Bioequivalence to the reference product was demonstrated by three bioequivalence studies at single dose under fed conditions. The studies were performed in healthy volunteers. Two studies were performed with both the 100 mg and the 400 mg strength film coated tablets and the third one with the 100 mg capsules.

The approved indication is:
"Imatinib Actavis 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 capsules, containing 50 mg or 100 mg and as film coated tables containing 100 mg or 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

Imatinib mesilate appears as a yellow to pale yellow amorphous hygroscopic powder, freely soluble in water. The chemical name of imatinib mesilate is 4-[(4-Methyl-1-piperazinyl) methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]aminophenyl] benzamide methanesulfonate salt. The molecular formula is $C_{29}H_{31}N_7O.CH_3SO_3H$ and its relative molecular mass 589.71 g/mol. Its pka is described as 7.9 and its pH 5.5 with LogP of 1.0

Imatinib mesilate exhibits polymorphism, the form manufactured by the proposed manufacturer is the amorphous form. There are no chiral centres and thus no stereoisomers exist.

Although the polymorphic form of active substance used in Actavis product differs from that of the reference product, there is no impact on the quality and performance of drug product because of the high aqueous solubility of all polymorphs.

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 in several well defined synthetic steps using commercially available starting materials. The route of synthesis was described in sufficient detail in the restricted part of the ASMF. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. Formation and presence of impurities, including potentially genotoxic ones, during manufacture has been satisfactorily discussed and shown that other than two they are not carried-over in the active substance. These two impurities, which are classified as genotoxic based on structure alerts, are derived from the process but they are also degradation products and at least one is a known metabolite.

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), solubility (visual inspection), identity (imatinib: IR, HPLC, XRPD, methane sulfonic acid: chemical reaction), assay (imatinib base: HPLC, methanesulphonic acid: (potentiometric titration), related substances (HPLC),

residual solvents (GC), water content (KF), residue on ignition (Ph. Eur.) heavy metals (Ph. Eur.) and microbial purity.

Impurities have been evaluated and found to be acceptable from a safety point of view. The proposed limitsfor genotoxic impurities are sufficiently discussed and were set considering the profile and progress of the disease, the relevant guidelines on Genotoxic impurities (EMEA/CHMP/QWP/251344/2006) and on Non-clinical Evaluation for Anticancer Pharmaceuticals (EMEA/CHMP/ICH/646107/2008) and the capability of the synthetic process. Therefore the set limits are considered justified. Furthermore, the possible formation of other possible genotoxic impurities was investigated and results from batch analysis demonstrate absence of same.

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

Batch analysis data on 3 commercial scale batches of the active substance were provided. The results comply with the specifications and confirm consistency and uniformity of the manufacturing process.

Stability

Stability studies have been conducted for three validation batches under ICH long term (5°C ± 3°C) and accelerated conditions (25°±2°C /60±5% RH). At long term conditions 18 months results were submitted, and very little change is seen. Although total impurities increase they still remain well within the specification and therefore the change is not considered significant. For the genotoxic impurities some fluctuation in value is observed but no real change is seen. Other tested parameters also remain unchanged. Similarly after 6 months at accelerated conditions of 25°±2°C the results were fully in line with the presented long term stability results.

<u>Forced degradation and photostability studies</u>
Degradation of the drug substance under extreme conditions was investigated under ambient, thermal, photolytic and humidity conditions for the solid state degradation study. In solution state hydrolysis at acidic, basic, and neutral conditions was explored, along with oxidative conditions.
Significant degradation was observed in solution state at acidic and oxidative conditions and at solution state mild reduction at basic and neutral conditions was seen. Hardly any degradation is found at solid state.
At both solid state and solution state, impurities (including genotoxic) are formed during the degradation study at thermal and high humidity conditions and increase is much more evident under acidic conditions and under basic and oxidative conditions. No change was documented when photostability is explored.
Based on the long-term stability data, the proposed re-test period and storage when the active substance is packed in the proposed packaging materials is considered acceptable.

2.2.3. Finished medicinal product

Pharmaceutical development

The aim of the development work was to formulate 100 mg and 400 mg imatinib tablets and 50 mg and 100 mg imatinib capsule intended to be similar to the reference drug product Glivec.

Film Coated Tablets

Imatinib mesylate is known to exist in several different polymorphic forms.The polymorphic form of imatinib used in the manufacture of tablets is defined and has been monitored and confirmed that it remains unchanged during the manufacturing and storage at 25°C and 40°C and under stressed conditions. All the excipients used in the formulation are described in the Ph. Eur. They are well known and widely used and are very similar to those of the reference product.

Several methods of manufacture have been explored from direct compression to wet and dry granulation. Dry granulation by roller compaction was selected for further development. Several lab batches were manufactured where the levels of different excipients were optimised. The same blend is used for the two strengths 100 and 400 mg by adjusting the tablet mass and dimensions in order to obtain proportional formulations.

Comparative dissolution studies have been performed in order to compare the dissolution profile for Imatinib Actavis 100 and 400 mg film-coated tablets and that of the reference product Glivec 100 and 400 mg tablets from EU market in different pH media (pH 1.2, 2.0, 4.5 and 6.8). The dissolution rates obtained were above 85% over the tested pH range for the single 100 mg film-coated tablets dose, slightly lower dissolution rates were obtained with the 400 mg film-coated tablets.

Finally, bioequivalence was demonstrated by two in vivo PK studies performed under fed conditions as per SmPC. The first study compared the Actavis 400 mg tablets versus the 400 mg reference product and the second one compared the Actavis 100 mg tablet strength against the same strength of the reference product.

Hard capsules

The same form of imatinib is used for the capsules as well and has also been confirmed that it remains unchanged during the manufacturing and storage at 25°C and 40°C and under stressed conditions. XRD tests were performed on the capsules. All the excipients used in the formulation are described in the Ph. Eur. They are well known and are very similar to those of the reference product and identical to Imatinib Actavis tablets. The main difference compared to reference capsules is that Imatinib Actavis capsules are made of hydroxypropylmethylcellulose instead of hard gelatin.

During development several techniques, various excipients, different forms of active substance were explored to optimize and develop a product that essentially was similar to the reference product Glivec. Dry granulation by roller compaction process was selected similar to that used for the tablets but optimised for capsule filling. Several lab batches were manufactured were lubricants, binders etc were explored.

Bioequivalence was demonstrated by an in vivo PK study performed under fed conditions as per SmPC, comparing the Actavis 100 mg capsule versus the 100 mg reference capsule. A biowaiver has been requested for the lower capsule strength supported by comparative dissolution results. All the biowaiver criteria as per the Bioequivalence Guideline were fulfilled. Comparative dissolution studies were conducted under conditions as recommended by Ph.Eur. 5.17.1 in aqueous media without the addition of enzymes. The capsules of both strengths show fast and complete dissolution for all tested pHs (1.2, 2.0, 4.5 and 6.8). Release is greater 85% after 15 min for both strengths. The biowaiver can therefore be accepted for the lower strength. In addition, a comparative dissolution study in three different pH media containing enzymes was also provided. This cannot be considered as a formal comparative dissolution study for the purpose of biowaiver because the use of enzymes is not allowed

by the Bioequivalence Guideline. However this was presented as supportive information. The reference product also dissolves easily at all the tested conditions. The results of the above in vitro dissolution studies also support the use of HPMC capsules.
Furthermore the proposed dissolution method used for quality control has been demonstrated to be discriminatory by performing the comparing dissolution profiles between one intentionally miss-manufactured batch and the biobatch/biowaiver batch.

Adventitious agents

None of the excipients used in the manufacture of either the tablets or the capsules are of human or animal origin. Appropriate BSE/TSE declarations from the manufacturers of excipients have been provided.

Manufacture of the product

Film Coated Tablets
The manufacturing process is a standard process comprising five steps including primary packaging. Smaller granulate batches are merged to one batch before compressing starts. There are no critical steps described, the process is a simple dry granulation and compression process. However, the process is controlled with appropriate in-process controls (IPC) which are acceptable for this pharmaceutical form.
Process validation has been performed on three submission batches of 100 mg and on three submission batches of 400 mg. The process was found to be well controlled producing consistent quality of the medicinal product that complies with the finished product specifications.

Hard Capsules
The manufacturing process is a standard process, similar as far as the blend preparation to that used for the tablets, comprising five steps including primary packaging. There are no critical steps; the process is a simple dry granulation and encapsulation process. The proposed IPCs are acceptable considering the pharmaceutical form. Process validation has been performed and results were presented on six consecutive batches showing that the manufacturing method is reproducible and robust and therefore considered validated yielding a medicinal product that complies with finished product specifications.

Product specification

Film Coated Tablets
The finished product release specifications include appropriate tests for appearance (visual examination), identification (HPLC and UV), assay (HPLC), uniformity of dosage unit (Ph. Eur.), related substances (HPLC), residual solvents (GC), identification of colorants (chemical reaction), dissolution (HPLC, Ph. Eur.), water content (Ph. Eur.) and microbiological quality (Ph. Eur.). Analytical methods have been well described and validated.

Hard Capsules
The finished product release specifications include appropriate tests for appearance of capsule and content (visual examination), identification (HPLC and UV), assay (HPLC), uniformity of dosage unit (Ph. Eur.), related substances (HPLC), identification of colorants (chemical reaction), dissolution (HPLC, Ph. Eur.), water content (Ph. Eur.) and microbiological quality (Ph. Eur.). Analytical methods have been well described and validated.

The proposed limits for the impurities are in accordance with the ICHQ3B guideline, whereas limits for known expected genotoxic impurities were set considering the profile and progress of the disease in accordance with the relevant guidelines on Genotoxic impurities (EMEA/CHMP/QWP/251344/2006) and on Non-clinical Evaluation for Anticancer Pharmaceuticals (EMEA/CHMP/ICH/646107/2008).

Stability of the product

Film Coated Tablets

Three (process validation) batches of each strength were placed on stability according to ICH guidance in both types of containers for marketing under the following conditions:
long term 25°C ±2°C / 60% ±5% RH, intermediate 30°C ±2°C / 65% ±5%RH and accelerated 40°C ±2°C / 75% ±5% RH.
18 months of data are available for the long term conditions in the two proposed packaging materials. The drug product is generally stable under long-term conditions in both containers. The only observable trends are a slight decrease in assay over time for both strengths and a gradual increase in one of the genotoxic impurities, which raises no concerns as remains still well within the set specifications. The levels of the other genotoxic impurity remain relatively constant. Furthermore, an increase in other impurities and total impurities can also be observed whereas dissolution remains constant over time for both tablet strengths. Water content seems to increase only in the tablets packaged in bottles. However, all data remain well within the specified limits.
Under intermediate conditions in both containers available stability results were fully in line with those obtained for the long term conditions.
Six month data (completed study) under accelerated conditions for both containers show formation of the expected genotoxic impurities and increase of total impurities. In addition other individual impurities go over specification limits. Water content also increases. Dissolution and assay remain stable. Other parameters comply with specifications.

In-use stability
Appropriate study has shown that the drug product is stable during the proposed in-use conditions (stored at 25°C ±2°C/60% R.H. ± 5 % R.H.) as stated in the SmPC.
Photo stability
The photo stability study was performed on drug product according to ICH guidelines and did not show signs of degradation after direct exposure to light and when not protected by the primary packaging material. The drug product (tablets) is stable under direct light exposure and is therefore considered to be non-photosensitive.
Based on the overall results the proposed shelf-life for tablets in blisters and bottles and the proposed storage condition are acceptable.

Hard Capsules

Three (process validation) batches of each strength were placed on stability according to ICH guidance in both types of containers for marketing under the following conditions:
long term 25°C±2°C / 60%±5% RH, intermediate 30°C±2°C / 65%±5%RH and accelerated 40°C±2°C / 75%±5% RH.
18 months of data are available for the long term conditions in the proposed packaging material. The drug product is generally stable under long-term conditions in both containers. The only observable trends are a gradual increase of the first genotoxic impurity, as well as “other impurities” and total impurities, which raises no concerns as they remain well within the specified limits. The levels for the other genotoxic impurity are relatively constant over time for both capsule strengths as is dissolution.

Under intermediate conditions available stability results were generally in line with those obtained for the long term conditions with the exception of a spike in the levels of an expected genotoxic impurity at the nine months time-point for all batches. However at the 12 months time point, the values are down to the normal level. Dissolution remains constant over time for both capsule strengths.
Six month data (completed study) under accelerated conditions show an increase in formation of the expected genotoxic impurities and increase of total impurities. Similarly to the tablets "other individual impurities" go over specification limits (OOS). Water content increases but dissolution and assay remain stable. Other parameters comply with specifications. Considering the above and the OOS results for both strengths during accelerated studies and that no significant change was observed during intermediate studies, an extrapolation of shelf-life of only up to three months beyond the period covered by long-term data can be granted.
Photostability
The photo stability study was performed on drug product according to ICH guidelines and did not show signs of degradation after direct exposure to light and when not protected by the primary packaging material. The drug product (capsules) has been shown to be stable under direct light exposure and is therefore considered to be non-photosensitive.
Based on the overall results the proposed shelf-life for capsules and the proposed storage condition are acceptable.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance has been presented in a satisfactory manner. There are some known expected impurities classified as genotoxic for which appropriate limits have been set in accordance with the guidelines. Sufficient information has been presented with regard to the development, manufacture and control of the finished product. The formulation, the choice of excipients including the type of capsule and their potential effect on the product performance has been extensively justified. The provided comparative dissolution studies are considered sufficient to support the biowaiver for the lower capsule strength and to demonstrate, together with the presented in vivo studies, consistent performance. 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 Actavis 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 conclusions 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 and hard capsules containing imatinib. To support the marketing authorisation application the applicant conducted three bioequivalence studies with cross-over design under fed conditions. These studies were pivotal studies 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. The studies were performed in compliance with GCP and GLP, including the archiving of essential documents and in compliance with the CROs SOPs. Various phases of the study were audited by the Quality Assurance department of the CRO, QA Statements are provided.

GCP and GLP regulatory inspections by EU inspectors have been performed at the relevant CRO.

Exemption

A biowavier for Imatinib Actavis 50 mg capsules is requested. Similarity of the in-vitro dissolution profiles of Imatinib Actavis 100 mg capsules and 50 mg capsules at pH 1.2, pH 2.0, pH 4.5 and pH 6.8 has been demonstrated. Therefore, the results of study IAI-P1-452 with 100 mg capsule formulation can be extrapolated to the other strength, 50 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr**, section 4.1.6.

Clinical studies

To support the application, the applicant has submitted three bioequivalence studies.

- **Study 1**
  Single Dose Crossover Comparative Bioavailability Study on Imatinib 100 mg Capsules in Healthy Male Volunteers / Fed State.
- **Study 2**
  Single Dose, 3-Way, Crossover Comparative Bioavailability Study of Imatinib 400 mg Film-Coated Tablets in Healthy Male Volunteers / Fed State.
- **Study 3**
  Single Dose Crossover Comparative Bioavailability Study of Imatinib 100 mg Film-Coated Tablets in Healthy Male Volunteers / Fed State

The bioequivalence studies were performed by a CRO. The protocols and informed consent forms were approved by an institutional review board (an independent Research Ethics Committee) prior to start of the studies.

Table 1. Tabular overview of clinical studies

Type of study	Study identifier	Objective(s) of the study	Study design and type of control	Test product(s); Dosage regimen; Route of administration	Nr of subjects	Healthy subjects or diagnosed patients	Duration of treatment	Study status; Type of report
BE	Study# 1	The objective of this study was to evaluate and compare the relative bioavailability and therefore the bioequivalence of two different formulations of imatinib capsules after a single 100 mg oral dose administration under fed conditions.	Crossover Fed state randomized, single dose, laboratory blinded, 2-period, 2-sequence	Imatinib capsule 100 mg single dose oral	24	Healthy subjects	Single dose	Complete; full

Type of study	Study identifier	Objective(s) of the study	Study design and type of control	Test product(s); Dosage regimen; Route of administration	Nr of subjects	Healthy subjects or diagnosed patients	Duration of treatment	Study status; Type of report
BE	Study# 2	The second objective of this study was to evaluate and compare the relative bioavailability and therefore the bioequivalence between the Test formulation of imatinib and the Reference-2 (EU Reference) after a single oral dose administration under fed conditions.	Crossover Fed state Single center, randomized, single dose, laboratory blinded, 3-period, 3-sequence,	Three tablet formulations; 400 mg single dose; oral	23	Healthy subjects	Single dose	Complete; full
BE	Study# 3	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	Crossover, Fed state	Two tablet formulations; 100 mg single dose; oral	24	Healthy subjects	Single dose	Complete; full

2.4.2. Pharmacokinetics

Study 1: Single Dose Crossover Comparative Bioavailability Study on Imatinib 100 mg Capsules in Healthy Male Volunteers / Fed State.

Methods

Study design

The bioequivalence study was a single centre, randomised, single dose, laboratory-blinded, 2-period, 2-sequence, crossover study design comparing Imatinib Actavis 100 mg hard capsules and Glivec 100 mg hard capsules in healthy male subjects under fed conditions.

The study was conducted between 6 and 26 August 2011, the dosing dates in period I and II were 7 and 21 August 2011, respectively. The clinical study report is signed and dated 12 October 2011.

Test and reference products

Product Characteristics	Test Product	Reference Product
Name	Imatinib Actavis 100 mg Hard Capsules	Glivec 100 mg Hard Capsules (from the German market)
Strength	100 mg	100 mg
Dosage form	Hard Capsules	Hard Capsules
Active ingredient	Imatinib Mesilate	Imatinib Mesilate
MAH	-	Novartis Europharm Limited, United Kingdom
Date of authorisation in the Community	-	7 November 2001

The certificates of analysis of the test and the reference products used in the bioequivalence study are provided.

The Imatinib Actavis 100 mg film-coated tablets used in the bioequivalence study are identical to the formulation intended to be marketed apart from a change in colouring agent requested by EMA.

Population(s) studied

A total of twenty-four (24) healthy white adult male volunteers (28-55 years; BMI 23.15-29.37 kg/m2), non- or ex-smokers, were included in the study. All twenty-four (24) subjects were included in the pharmacokinetic and statistical analysis as well as safety analysis.

Analytical methods

A valid reverse-phase HPLC with MS/MS detection was employed in determining sample concentration of imatinib in human plasma. K2EDTA was used as anticoagulant. The internal standard used is Imatinib-D8. The method is valid with respect to selectivity, specificity (also in the presence of concomitantly administered compounds), sensitivity (LOQ QC 10.0 ng/ml), linearity, between-run and within-run accuracy and precision, matrix effect (also the impact of hemolysis and the presence of lipids), dilution integrity (5x dilution of twice the ULQ), recovery, re-injection reproducibility and stability (short term in solution, plasma and whole blood; long term in solution and plasma; freeze thaw in plasma; processed reconstituted). No significant carryover was observed. The initial calibration curve range used in the validation was 10.0 to 4000.0 ng/ml. A partial validation was conducted for a truncated concentration range, 10.0 – 1000.0 ng/ml, and additional quality control (QC) sample level (350.0 ng/ml) was added. The results for precision, accuracy, dilution integrity and linearity show that the method is also valid over the truncated concentration range, 10.0-1000.0 ng/ml.

The analytical report is signed and dated 29 September 2011. Plasma samples were stored at -20°C and were received frozen by Algorithme Pharma´s analytical facility. Sample pre-treatment involved the liquid-liquid extraction of imatinib from human plasma. A total of 960 samples were received and analysed and the number of repeat samples is 13 (1.4%) due to unexpected internal standard response. Incurred sample reproducibility was successfully assessed. The performance of the method was acceptable during study sample analysis. The storage period of the study samples was 36 days. Long term stability of imatinib in plasma was confirmed up to 837 days at -20°C nominal. No missing samples for the subjects included in the statistical analysis were observed. There was no protocol, bioanalytical plan or significant SOP deviations.

Pharmacokinetic variables

The main pharmacokinetic parameters of interest for this study were to be Cmax and AUC0-t. Other parameters such as Tmax, AUC0-∞, AUCT/∞, Kel and T½el were to be provided for information purposes only. A non-compartmental approach was used and standard methods to calculate the pharmacokinetic parameters.

Statistical methods

Statistical and pharmacokinetic analyses were generated using Kinetic, version 9.01, an application developed by the CRO and SAS version 9 (GLM procedure).

The natural logarithmic transformation of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ was to be used for all statistical inference.

The parameter Tmax was analysed using a non-parametric approach. Test of fixed period, sequence and treatment effects were to be based on the Wilcoxon´s rank sum test (Mann-Whitney U-test). When appropriate (e.g. small or sparse sample), the exact version of the test was also to be presented.

All other un-transformed and ln-transformed pharmacokinetic parameters were to be statistically analysed using an Analysis of Variance (ANOVA) model. The fixed factors included in this model were the subject effect (nested within sequence), the treatment received, the period at which it was given as well as the sequence in which each treatment was being received. The sequence, period and treatment effects were to be assessed at the 5% two-sided level.

Criteria for Bioequivalence

Bioequivalence was to be declared if the ratio of geometric LS means with corresponding 90% confidence interval calculated from the exponential of the difference between the Test and Reference product for the ln-transformed parameters Cmax and AUC_{0-t} were all to be within the 80.00 to 125.00% bioequivalence range.

Results

Table 2: Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	**AUC_{0-t}** ng/ml/h	**$AUC_{0-\infty}$** ng/ml/h	**C_{max}** ng/ml	**t_{max}** h
Test	7378.9 ± 2400.9	7802.0 ± 2581.8	442.1 ± 138.8	5.00 (2.67-10.00)
Reference	6655.4 ± 2138.8	7045.5 ± 2314.9	400.8 ± 123.3	4.50 (3.50-8.00)
***Ratio (90% CI)**	110.64% (107.15%-114.23%)	110.55% (107.12%-114.09%)	110.19% (104.88%-115.76%)	-

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t. AUC_{0-72h} can be reported instead of AUC_{0-t}, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time. $AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}
C_{max} Maximum plasma concentration
t_{max} Time until Cmax is reached
**ln-transformed values*

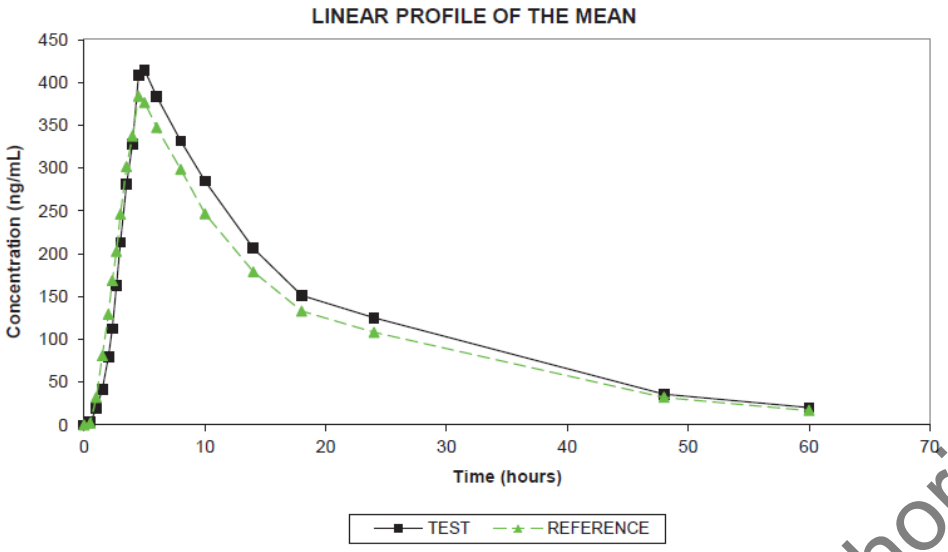

Figure 1: Linear profile of the mean imatinib plasma concentration versus time (n=24).

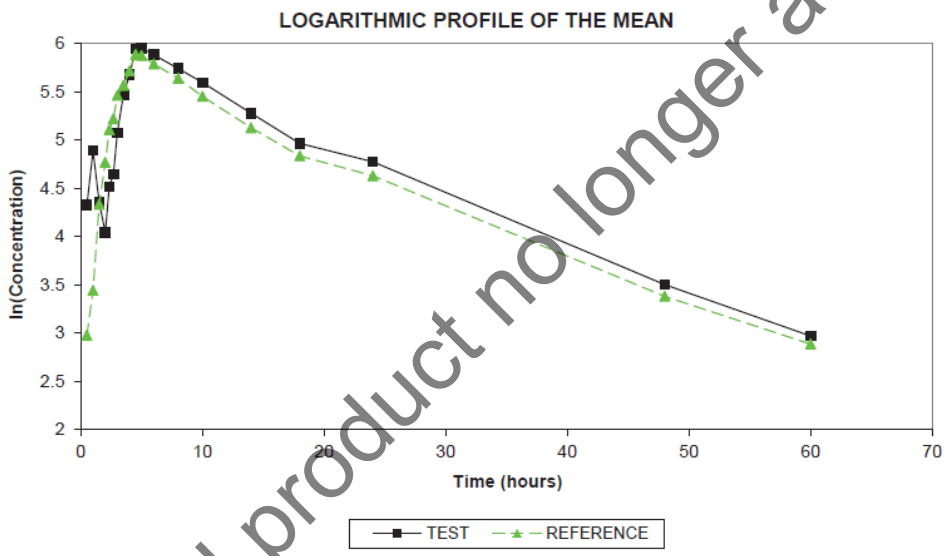

Figure 2: Logarithmic profile of the mean imatinib plasma concentration versus time (n=24).

The Test to Reference ratio of geometric LSmeans and corresponding 90% confidence interval for the C_{max} and AUC_{0-t} were all within the acceptance range of 80.00 to 125.00%.

In vitro dissolution

The dissolution studies were conducted using paddles, and media as per chapter 5.17.1 Section: Recommendations on dissolution testing of European Pharmacopeia. A biowavier for the Imatinib Actavis 50 mg capsules is requested. The dissolution studies conducted showed similarity in dissolution between one capsules Imatinib Actavis 100 mg capsule vs. two capsules Imatinib Actavis 50 mg capsule at pH 1.2, pH 2.0, pH 4.5 (acetate buffer solution) and pH 6.8 (phosphate buffer solution) with more than 85% dissolved in 15 minutes. The results of study 1 with 100 mg capsule formulation can be extrapolated to the other strength, 50 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr**, section 4.1.6.

Comparative dissolution studies complementary to the bioequivalence study on the biobatches, Imatinib Actavis 100 mg capsules and Glivec 100 mg capsules, were not conducted using the same dissolution conditions.

Safety data

Seven (7) (29.2%) of the twenty-four (24) subjects included in this study experienced a total of sixteen (16) adverse events (AEs). Five (5) subjects (20.8%) reported 8 AEs after the single doseadministration of the Test product and 5 subjects (20.8%) reported 8 AEs after the single dose administration of the Reference product. The severity of AEs was mild or moderate. No severe AEs were observed during the study. None of the AEs judged to be possibly related to the Investigational Products were unexpected. No serious AEs or deaths were reported during the study. No AEs required the use of medications and no subject was withdrawn from the study for safety reasons. No clinically significant post-dose laboratory values were recorded during the study. Overall, the drugs tested were generally safe and well tolerated by the subjects included in this study.

Conclusions

Based on the bioequivalence study 1, Single Dose Crossover Comparative Bioavailability Study on Imatinib 100 mg Capsules in Healthy Male Volunteers / Fed State, Imatinib Actavis 100 mg capsules are considered bioequivalent with Glivec 100 mg capsules. The results of study 1with 100 mg capsule formulation can be extrapolated to the other strength, 50 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr**, section 4.1.6.

Study 2: Single Dose, 3-Way, Crossover Comparative Bioavailability Study of Imatinib 400 mg Film-Coated Tablets in Healthy Male Volunteers / Fed State.

Methods

Study design

The bioequivalence study was a single center, randomised, single dose, laboratory-blinded, 3-period, 3-sequence, crossover design comparing Imatinib Actavis 400 mg film-coated tablets and Glivec 400 mg film-coated tablets performed in healthy male subjects under fed conditions.

The study was conducted between 12 April and 26 May 2011, the dosing dates in period I, II and III were 13 April 2011, 27 April 2011 and 11 May 2011, respectively. The clinical study report is signed and dated 19 July 2011.

Test and reference products

Product Characteristics	**Test Product**	**Reference Product (Reference-2)**
Name	Imatinib Actavis 400 mg Film-Coated Tablet	Glivec 400 mg Film-Coated Tablet (from the German market)
Strength	400 mg	400 mg
Dosage form	Film-Coated Tablet	Film-Coated Tablet
Active ingredient	Imatinib Mesilate	Imatinib Mesilate
MAH	-	Novartis Europharm Limited, United Kingdom
Date of authorisation in the Community	-	7 November 2001

The certificates of analysis of the test and the reference products used in the bioequivalence study are provided.

The Imatinib Actavis 100 mg film-coated tablets used in the bioequivalence study are identical to the formulation intended to be marketed apart from a change in colouring agent requested by EMA. ***Population(s) studied***

A total of twenty-four (24) healthy adult male volunteers (22-54 years; BMI 20.46-29.93 kg/m2; 22 white and 2 black), non- or ex-smokers, were included in the study and analysed. Twenty-three (23) subjects were included in the pharmacokinetic and statistical analysis but all twenty-four (24) subjects in the safety analysis. Subject #010 was withdrawn from period 2 since the critical breakfast was not completed within 30 minutes and then the subject withdrew consent from the study before dosing of period 3 (not related to clinical event). Subject #010 was excluded from the pharmacokinetic and statistical analysis because he did not provide evaluable data for the treatments of interest.

Analytical methods

A validated reverse-phase HPLC with MS/MS detection was employed in determining sample concentration of imatinib in human plasma. K2EDTA was used as anticoagulant. The internal standard used is Imatinib-D8.The calibration curve range used during study sample analysis was 10.0 – 4000.0 ng/ml. In order to have QC concentration levels that reflect the majority of study sample concentrations, an additional QC level (1100.0 ng/ml) was prepared and incorporated into study sample batches. The analytical report is signed and dated 13 July 2011. Plasma samples stored at -20°C and received frozen by the CRO analytical facility. A total of 1361 samples were received and analysed and the number of repeat samples is 15 (1.1%) due to unexpected internal standard response, concentration above upper limit of quantitation and sample lost in processing. Incurred sample reproducibility was successfully assessed. The performance of the method was acceptable during study sample analysis. The storage period of the study samples was 48 days. Long term stability of imatinib in plasma was confirmed up to 837 days at -20°C nominal. No missing samples for the subjects included in the statistical analysis were observed. There was no protocol, bioanalytical plan or significant SOP deviations.

Pharmacokinetic variables

The main pharmacokinetic parameters of interest for this study were to be Cmax and AUC0-t. Other parameters such as Tmax, AUC0-∞, AUCT/∞, Kel and T½el were to be provided for information purposes only. A non-compartmental approach was used and standard methods to calculate the pharmacokinetic parameters.

Statistical methods

Statistical and pharmacokinetic analyses were generated using Kinetic, version 9.01, an application developed by the CRO and SAS version 9 (GLM procedure). The natural logarithmic transformation of Cmax, AUC0-t and AUC0-∞ as well as the rank-transformation of Tmax were to be used for all statistical inference.

All un-transformed and ln-transformed pharmacokinetic parameters were to be statistically analysed using an Analysis of Variance (ANOVA) model. The fixed factors included in this model were to be the subject effect (nested within the sequence), the treatment received, the period at which it was given, the sequence in which each treatment was being received as well as the left-

over interaction terms between the four factors. A lack of fit test was to be performed using the three-way interaction terms. When the lack of fit test is rejected at the 5% level, the parameters were to be analysed using the saturated model. When this test is not rejected, the three-way interaction terms were to be removed from the model. The sequence, period and treatment effects were to be assessed at the 5% two-sided level.

Criteria for Bioequivalence

Bioequivalence was to be declared if the ratio of geometric LS means with corresponding 90% confidence interval calculated from the exponential of the difference between the Test and Reference-2 product for the ln-transformed parameters Cmax and AUC_{0-t} were all to be within the 80.00 to 125.00% bioequivalence range.

Results

Table 3: Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	**AUC_{0-t}** ng/ml/h	**$AUC_{0-\infty}$** ng/ml/h	**C_{max}** ng/ml	**t_{max}** h
Test	38587.7 ± 13149.0	39734.5 ± 13671.0	2349.5 ± 939.5	3.50 (2.00-5.00)
Reference	36514.9 ± 13017.8	37601.3 ± 13471.5	2194.5 ± 816.2	3.00 (1.50-10.00)
***Ratio (90% CI)**	106.52% (103.00%-110.16%)	106.46% (102.99%-110.05%)	105.75% (100.61%-111.15%)	-

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t. AUC_{0-72h} can be reported instead of AUC_{0-t}, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time. $AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}
C_{max} Maximum plasma concentration
t_{max} Time until Cmax is reached
**ln-transformed values*

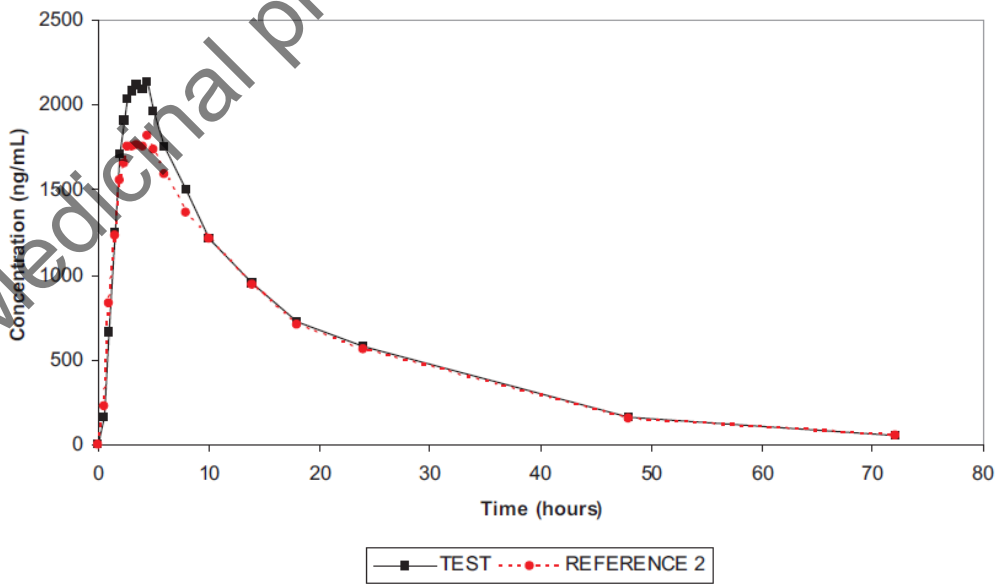

Figure 3: Linear profile of the mean imatinib plasma concentration versus time (n=23).

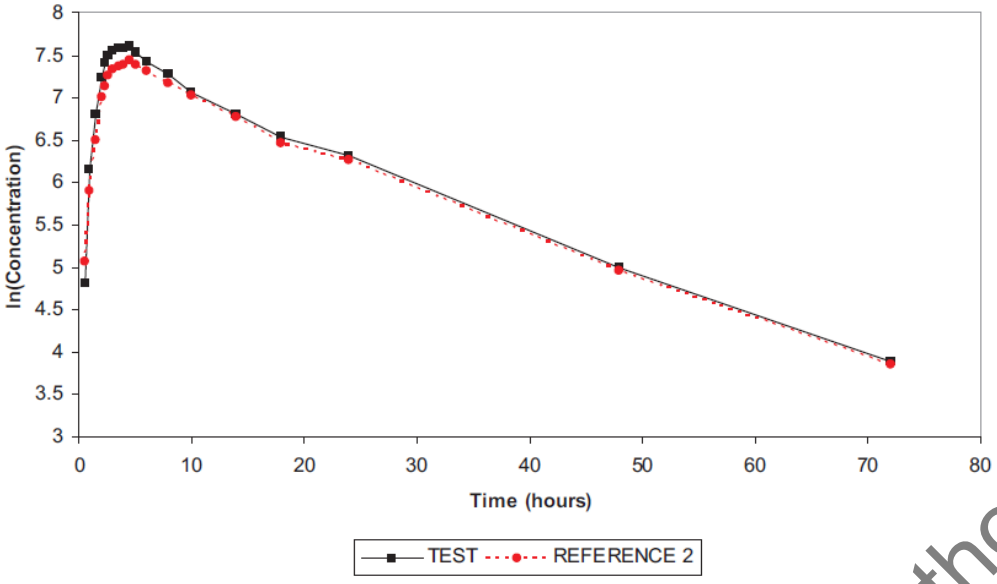

Figure 4: Logarithmic profile of the mean imatinib plasma concentration versus time (n=23).

The Test to Reference ratio of geometric LSmeans and corresponding 90% confidence interval for the Cmax and AUC0-t were all within the acceptance range of 80.00 to 125.00%.

In vitro dissolution

Comparative dissolution studies (paddles, dissolution media according to 4.1.3 Section Buffer from European Pharmacopeia) were conducted at pH 1.2, 2.0, 4.5 and 6.8 on the batches used in the bioequivalence study, Imatinib Actavis 400 mg film-coated tablets and Glivec 400 mg film-coated tablets. The bioequivalence study showed that the two products are bioequivalent. An additional bioequivalence study was submitted for the 100 mg film-coated tablets and therefore a biowaiver is not requested for the 100 mg film-coated tablets.

Safety data

Fourteen (14) (58.3%) of the twenty-four (24) subjects included in this study experienced a total of forty-four (44) AEs after administration of the Test, Reference-1 (US reference product) and Reference-2 (EU reference product). Five (5) subjects (21.7%) reported 10 AEs after the single dose administration of the Test product and 8 subjects (34.8%) reported 12 AEs after the single dose administration of the Reference-2 product. The severity of AEs ranged from mild to severe. One (1) severe AE (Reference-2: salivary hypersecretion) were observed during the study. Of all AEs, 1 (salivary hypersecretion) was unexpected and possibly related to the administration of the Reference-2 product. No serious AEs or deaths were reported during this study. No subject took concomitant medications during the study. No subject was withdrawn from the study for safety reasons. Two (2) subjects (no. 006 and 024) had abnormal clinically significant laboratory values at post-study that were reported as AEs. Overall, the drugs tested were generally safe and well tolerated by the subjects included in this study.

Conclusions

Based on the bioequivalence study 2, Single Dose, 3-Way, Crossover Comparative Bioavailability Study of Imatinib 400 mg Film-Coated Tablets in Healthy Male Volunteers / Fed State, Imatinib Actavis 400 mg film-coated tablets are considered bioequivalent with Glivec 400 mg film-coated tablets.

Study 3: Single Dose Crossover Comparative Bioavailability Study of Imatinib 100 mg Film-Coated Tablets in Healthy Male Volunteers / Fed State.

Methods

Study design

The study was conducted between 2012/07/20 and 2012/08/08 (dosing dates 2012/07/21 and 2012/08/04 for period 1 and 2, respectively) by a CRO. The clinical study report is signed and dated in September 2012. The bioequivalence study was a single center, randomized, single dose, laboratory-blinded, 2-period, 2-sequence, crossover design comparing Imatinib Actavis 100 mg film-coated tablets and Glivec 100 mg film-coated tablets performed in healthy male subjects under fed conditions.

Test and reference products

Product Characteristics	Test Product	Reference Product
Name	Imatinib Actavis 100 mg Film-coated tablets	Glivec 100 mg Film-coated tablets (from the German market)
Strength	100 mg	100 mg
Dosage form	Film-coated tablets	Film-coated tablets
Active ingredient	Imatinib Mesilate	Imatinib Mesilate
MAH	-	Novartis Europharm Limited, United Kingdom
Date of authorisation in the Community	-	7 November 2001

The certificates of analysis of the test and the reference products used in the bioequivalence study are provided.

The Imatinib Actavis 100 mg film-coated tablets used in the bioequivalence study are identical to the formulation intended to be marketed apart from a change in colouring agent requested by EMA.

Population(s) studied

A total of 24 healthy adult male volunteers (19 White, 3 Black and 2 Asian), non- or ex-smokers, ranged in age from 27 to 54 years and body mass indices (BMI) within 22.25 – 28.57 kg/m2 were included in this trial following pre-study screening procedures and signing of the written consent form. The subjects were in good health according to the inclusion and exclusion criteria outlined in the protocol. All twenty-four (24) subjects completed the crossover design and were analyzed and included in the pharmacokinetic and statistical analysis. There were two missing samples (48.00 hours, period 1 and 2 for subject 004).

Analytical methods

The study blood samples were collected in pre-cooled K2EDTA vacutainers. Sample pre-treatment involved the liquid-liquid extraction of Imatinib from human plasma. Imatinib-D8 was used as the internal standard. The compounds were identified and quantified using reversed-phase HPLC with MS/MS detection over a theoretical concentration range of 10.0 ng/ml to 1000.0 ng/ml.

Validation

The HPLC with MS/MS detection method for the determination of Imatinib in human plasma was validated and has met acceptance criteria with respect to selectivity, specificity (also in the presence of concomitantly administered compounds), sensitivity, linearity range (10.0 ng/ml to 1000.0 ng/ml for Imatinib), between-run and within-run accuracy and precision, matrix effect, percent extraction yields, dilution integrity and stability in matrix and solutions. Long-term stability of Imatinib in human plasma has been determined for 837 days at -20°C. The lower limit of quantitation (LOQ) and upper limit of quantitation (ULQ) were 10.0 ng/mL and 1000.0 ng/mL, respectively. The LOQ signals were >5 times the height of the baseline noise. The QC sample concentrations of Imatinib were 10.0 ng/ml, 30.0 ng/ml, 350.0 ng/ml and 750.0 ng/ml. No significant carryover was observed in all accepted batches, nor was anticipated using the analytical method. There were no significant SOP deviations.

Bioanalysis

The bioanalytical report dated 2012/08/31 is provided.

The plasma samples were received frozen by Algorithme Pharma´s analytical facility and stored at -20°C nominal. The subject plasma sample analysis was performed between 2012/08/16 and 2012/08/22, including re-assays and incurred samples.

The calibration range used during subject sample analysis was 10.0 ng/mL- 1000.0 ng/mL. The QC sample concentrations were 30.0 ng/ml, 100.0 ng/ml, 200.0 ng/ml, 350.0 ng/ml and 750 ng/ml. The 100.0 ng/ml and 200.0 ng/ml QC levels were added in order to have the QC concentration levels reflect the majority of study sample concentrations. Carryover was evaluated prior to the injection of every batch and must be deemed not signifanct. No significant carryover was observed in all accepted batches, nor was anticipated using the analytical method.

The number of samples analysed was 958 and the number of repeat samples due to sample lost in processing was 3 (0.3% of total analysed samples).

Incurred sample reproducibility was successfully determined. At least 10% of the total analysable subject samples were re-assayed and compared to the original values and at least 2/3 of the total samples selected met the criteria of percent difference ⩽20.0%.

The period from the first sample collection (2012/07/21) until completion of sample analysis (2012/08/22) was 32 days.

Chromathograms for 20% of the subjects were provided.

There were no protocol, Bioanalytical Plan or significant SOP deviations.

Pharmacokinetic Variables

The main pharmacokinetic parameters of interest for this study were to be Cmax and AUC0-t. Other parameters such as Tmax, AUC0-∞, AUCT/∞, Kel and T½el were to be provided for information purposes only. A non-compartmental approach was used and standard methods to calculate the pharmacokinetic parameters.

Statistical methods

The statistical analysis was carried out according to the bioequivalence guidelines. Statisical analysis of T_{max} was based on a non-parametric approach. All other pharmacokinetic parameters were statistically analysed using a parametric Analysis of Variance (ANOVA) model. The fixed factors included in this model were subject effect (nested within the sequence), the treatment received, the period at which it was given, the sequence in which each treatment was being received as well as the left-over interaction terms between the four factors. Furthermore, the two-sided 90% confidence interval for the exponential of the difference in LSmeans between Test and Reference product was calculated for the ln-transformed parameters (Test to Reference ratio of geometric LSmeans).

Criteria for Bioequivalence

Bioequivalence was to be declared if the ratio of geometric LSmeans with corresponding 90% confidence interval calculated from the exponential of the difference between the Test and Reference product for the ln-transformed parameters C_{max} and AUC_{0-t} were all within the 80.00 to 125.00% bioequivalence range.

Results

Table 4: Pharmacokinetic parameters for imatinib (non-transformed values)

Pharmacokinetic parameter	Test Arithmetic mean	±SD CV%	Reference Arithmetic mean	±SD CV%
$AUC_{(0-t)}$ (ng·h/ml)	6413.69	±1715.22 26.7%	6356.06	±1548.91 24.4%
$AUC_{(0-\infty)}$ (ng·h/ml)	6724.52	±1744.47 25.9%	6665.23	±1558.91 23.4%
C_{max} (ng/ml)	430.42	±165.26 38.4%	415.96	±139.95 33.6%
T_{max}* (hours)	2.875	(1.00-5.00) 41.5%	3.75	(1.00-5.00) 36.9%

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
C_{max} maximum plasma concentration
T_{max} time for maximum concentration (* median, range)

Statistical analysis for imatinib (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference (%)	Confidence Intervals (%)	CV%*
$AUC_{(0-t)}$	100.40	96.60-104.36	N/AV
C_{max}	102.46	95.61-109.80	N/AV

* estimated from the Residual Mean Squares

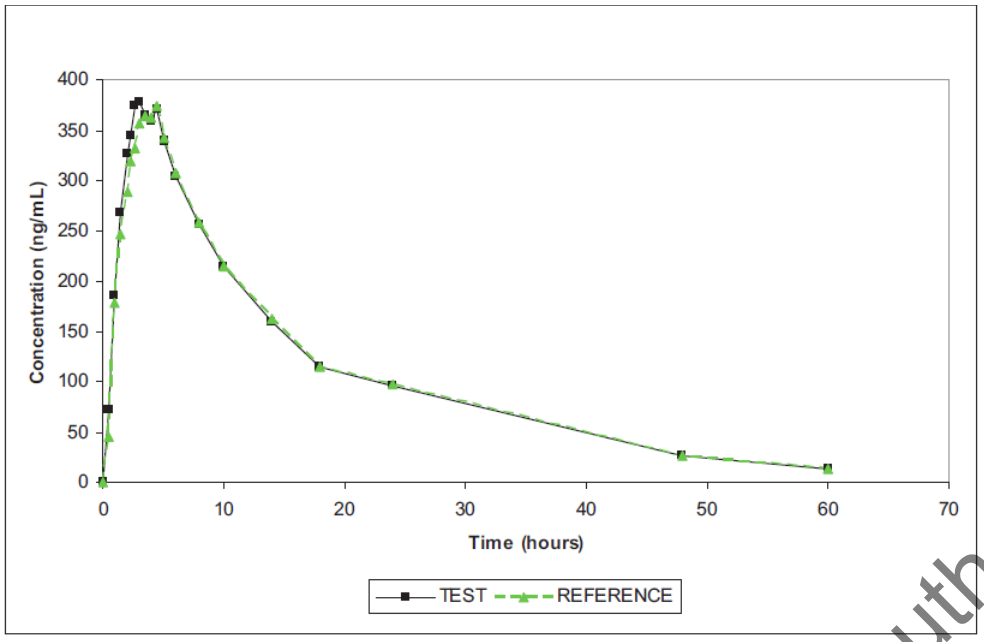

Figure 5: The mean measured imatinib plasma concentration versus time profile, derived from the administration of the Test and Reference products (N=24).

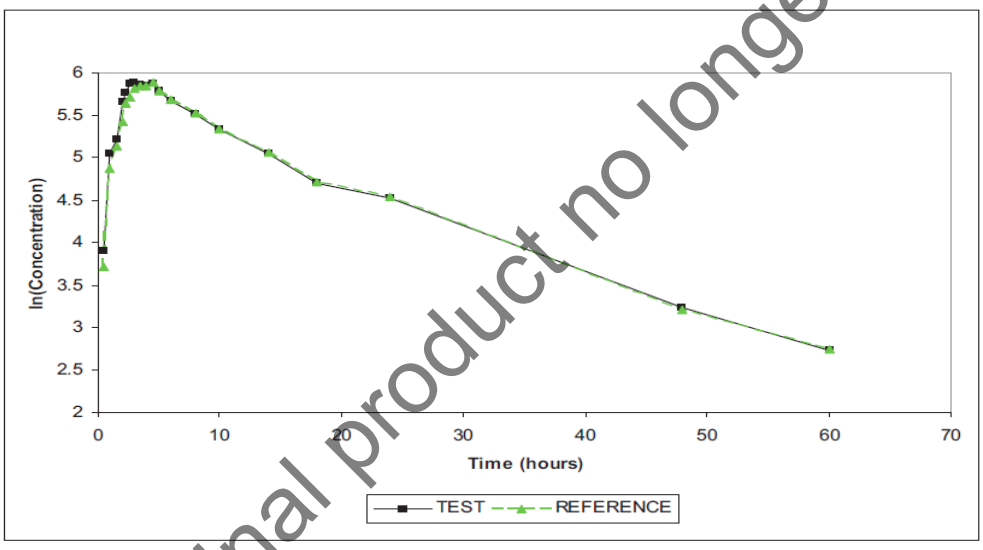

Figure 6: The ln-transformed mean imatinib plasma concentration versus time profile, derived from the administration of the Test and Reference products (N=24).

The results presented herein show that the criteria used to assess bioequivalence between the Test and Reference formulations were all fulfilled. The Test to Reference ratio of geometric LSmeans and corresponding 90% confidence interval for the Cmax, AUC0-t and AUC0-∞ were all within the pre-specified bioequivalence acceptance ranges of 80.00% to 125.00%.

In vitro dissolution

The dissolution studies were conducted using paddles, with JP sinkers and media as per chapter 5.17.1 Section: Recommendations on dissolution testing of European Pharmacopeia. The setup was improved from the initial setup by increasing the paddle speed and changing the media.

The dissolution profiles of the 100 mg film-coated test and the reference biobatches were found to be similar with more than 85% of the label amount dissolved within 15 min at pH 1.2, 2.0, 4.5 and 6.8 and a low RSD%.

Safety data

Fourteen (14) (58.3%) of the 24 subjects included in the study experienced a total of 29 adverse events (AEs). Seven (7) subjects (29.2%) reported 12 AEs after the single dose administration of the test product and 11 subjects (45.8%) reported 17 AEs after the single dose administration of the reference product. The severities of AEs were mild to moderate. No severe AEs were observed during the study. No AEs required the use of medications following the first dosing. No subject was withdrawn from the study for safety reasons. Overall, the drugs tested were generally safe and well tolerated by the subjects included in this study.

Conclusions

Based on the additional bioequivalence study 3, Single Dose Crossover Comparative Bioavailability Study of Imatinib 100 mg Film-Coated Tablets in Healthy Male Volunteers / Fed State, Imatinib Actavis 100 mg film-coated tablets are considered bioequivalent with Glivec 100 mg film-coated tablets.

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 clinical overview on the clinical pharmacology, efficacy and safety is considered adequate.

To support the application, the applicant initially submitted two (2) bioequivalence studies (Study 1 and Study 2) . One additional bioequivalence study (Study 3)was submitted to support the application.

Based on the bioequivalence study 1, Single Dose Crossover Comparative Bioavailability Study on Imatinib 100 mg Capsules in Healthy Male Volunteers / Fed State, Imatinib Actavis 100 mg capsules are considered bioequivalent with Glivec 100 mg capsules. The results of study 1 with 100 mg capsule formulation can be extrapolated to the other strength, 50 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr**, section 4.1.6.

Based on the bioequivalence study 2, Single Dose, 3-Way, Crossover Comparative Bioavailability Study of Imatinib 400 mg Film-Coated Tablets in Healthy Male Volunteers / Fed State, Imatinib Actavis 400 mg film-coated tablets are considered bioequivalent with Glivec 400 mg film-coated tablets.

Based on the additional bioequivalence study 3, Single Dose Crossover Comparative Bioavailability Study of Imatinib 100 mg Film-Coated Tablets in Healthy Male Volunteers / Fed State, Imatinib Actavis 100 mg film-coated tablets are considered bioequivalent with Glivec 100 mg film-coated tablets.

The in vitro dissolution method has been optimised and the dissolution tests complementary to the bioequivalence study on the 100 mg film-coated tablet formulations show that the dissolution of the test and the reference biobatches are similar.

The dissolution methods were optimised and the dissolution test show that the dissolution of the Imatinib Actavis film-coated tablets and capsules formulations are independent of pH and therefore there should not be a risk of reduced bioavailability of the Imatinib Actavis formulations in comparison to Glivec in patients with low gastric acid production (e.g. due to the intake of PPIs).

The test and the reference products were generally safe and well tolerated by the subjects included in the bioequivalence studies.

2.4.6. Conclusions on clinical aspects

The CHMP considers Imatinib Actavis 50 mg and 100 mg capsules approvable from the clinical point of view.

The CHMP considers Imatinib Actavis 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 (Module 1.8.1) 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.

The CHMP also recommended the applicant to monitor use during pregnancy; tolerability during pregnancy and pregnancy outcomes (if applicable/available).

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

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.

3. Benefit-risk balance

This application concerns a generic version of Imatinib film-coated tablets and hard capsules. The reference product is Glivec.

No non-clinical studies have been provided for this application but an adequate summary of the available non-clinical 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 dose crossover comparative bioavailability study for the capsules and a single dose, 3-way, crossover comparative bioavailability study for the film-coated tablets. The studies designs were considered adequate to evaluate the bioequivalence of these formulations and were in line with the respective European requirements. Bioequivalence studies were conducted in male volunteer patients in the fed status. 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 Actavis 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.

4. Recommendation

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Imatinib Actavis is not similar to Tasigna and Sprycel within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See the CHMP Assessment Report for Imatinib Actavis on similarity with Tasigna and Sprycel (appendix I).

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Imatinib Actavis 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.

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",
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.