14 September 2017
EMA/652456/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Imatinib Teva B.V.

International non-proprietary name: imatinib

Procedure No. EMEA/H/C/004748/0000

Note

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

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List of abbreviations

BCS	Biopharmaceutics Classification System
CEP	Certificate of Suitability of the EP
CFU	Colony Forming Units
DSC	Differential Scanning Calorimetry
EDQM	European Directorate for the Quality of Medicines
EC	European Commission
GC	Gas Chromatography
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPC	In-process control
JP	Japanese pharmacopoeia
KF	Karl Fischer titration
NF	National Formulary
OPA	Oriented polyamide
PE	Polyethylene
Ph. Eur.	European Pharmacopoeia
PVC	Polyvinyl chloride
PVdC	Polyvinylidene chloride
QC	Quality control
q.s.	*Quantum satis*
RH	Relative Humidity
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
USP	United States Pharmacopoeia
UV	Ultraviolet
XRPD	X-Ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Teva B.V. submitted on 5 April 2017 an application for marketing authorisation to the European Medicines Agency (EMA) for Imatinib Teva B.V., 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 February 2017.

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, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in 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 Teva B.V. 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.
- Adult and paediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) integrated with chemotherapy.
- Adult patients with relapsed or refractory Ph+ ALL as monotherapy.
- Adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements.
- Adult patients with advanced hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL) with FIP1L1-PDGFRα rearrangement.

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

Imatinib Teva B.V. is indicated for

- The treatment of adult patients with Kit (CD 117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST).
- The adjuvant treatment of adult patients who are at significant risk of relapse following resection of Kit (CD117)-positive GIST. Patients who have a low or very low risk of recurrence should not receive adjuvant treatment.
- The treatment of adult patients with unresectable dermatofibrosarcoma protuberans (DFSP) and adult patients with recurrent and/or metastatic DFSP who are not eligible for surgery.

In adult and paediatric patients, the effectiveness of imatinib is based on overall haematological and cytogenetic response rates and progression-free survival in CML, on haematological and cytogenetic response rates in Ph+ ALL, MDS/MPD, on haematological response rates in HES/CEL and on objective response rates in adult patients with unresectable and/or metastatic GIST and DFSP and on recurrence-free survival in adjuvant GIST. The experience with imatinib in patients with MDS/MPD associated with PDGFR gene re-arrangements is very limited (see section 5.1). There are no controlled trials demonstrating a clinical benefit or increased survival for these diseases.

The legal basis for this application refers to:

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

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

This application is submitted as a multiple of Imatinib Teva authorised on 08/01/2013 in accordance with Article 82.1 of Regulation (EC) No 726/2004. The submission of this application is due to patent grounds.

The chosen reference product is:

Medicinal product which is or has been authorised 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 number(s): EU/1/01/198/009, EU/1/01/198/010 and EU/1/01/198/013

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

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.

Scientific advice

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP were:

Rapporteur: Jorge Camarero Jiménez Co-Rapporteur: N/A

- The application was received by the EMA on 5 April 2017.
- The procedure started on 24 April 2017.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 31 May 2017.
- The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 31 May 2017.
- During the meeting on 9 June 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the meeting on 22 June 2017, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 13 July 2017.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 24 August 2017.
- During the PRAC meeting on 1 September 2017, the PRAC agreed on a PRAC Assessment Overview and Advice to CHMP.
- During the meeting on 14 September 2017, 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 Teva B.V.

2. Scientific discussion

2.1. Introduction

Imatinib Teva BV 100 mg and 400 mg film-coated tablet and 100 mg and 400 mg hard capsules is a duplicate application to Imatinib Teva and generic of Glivec.

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 and acute lymphoblastic leukaemia (ALL) patients.

The approved indication is:

Imatinib Teva B.V. 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.
- Adult and paediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) integrated with chemotherapy.
- Adult patients with relapsed or refractory Ph+ ALL as monotherapy.
- Adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements.
- Adult patients with advanced hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL) with FIP1L1-PDGFRα rearrangement.

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

Imatinib Teva B.V. is indicated for

- The treatment of adult patients with Kit (CD 117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST).
- The adjuvant treatment of adult patients who are at significant risk of relapse following resection of Kit (CD117)-positive GIST. Patients who have a low or very low risk of recurrence should not receive adjuvant treatment.
- The treatment of adult patients with unresectable dermatofibrosarcoma protuberans (DFSP) and adult patients with recurrent and/or metastatic DFSP who are not eligible for surgery.

In adult and paediatric patients, the effectiveness of imatinib is based on overall haematological and cytogenetic response rates and progression-free survival in CML, on haematological and cytogenetic response rates in Ph+ ALL, MDS/MPD, on haematological response rates in HES/CEL and on objective response rates in adult patients with unresectable and/or metastatic GIST and DFSP and on recurrence-free survival in adjuvant GIST. The experience with imatinib in patients with MDS/MPD associated with PDGFR gene re-arrangements is very limited (see section 5.1). There are no controlled trials demonstrating a clinical benefit or increased survival for these diseases.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tables and hard capsules containing 100 mg and 400 mg of imatinib (as mesylate salt) as active substance.

Other ingredients are:

Film-coated tablets:

Tablet core: anhydrous calcium hydrogen phosphate, crospovidone and magnesium stearate

Tablet coat: partially hydrolysed polyvinyl alcohol, macrogol, iron oxide yellow (E172), talc, titanium dioxide (E171) and iron oxide red (E172)

Hard capsules:

Capsule fill: mannitol, crospovidone, magnesium stearate and anhydrous colloidal silica

Capsule shell: gelatin, titanium dioxide (E171), iron oxide yellow (E172) and iron oxide red (E172)

Printing ink: shellac, iron oxide black (E172) and propylene glycol

The product is available in PVC/PE/PVdC/PE/PVC/Al or OPA/Al/PVC/Al blisters as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of imatinib mesylate is 4-[(4-methylpiperazin-1-yl)methyl]-*N*-(4-methyl-3-[[4-(pyridin-3-yl)pyrimidin-2-yl]amino]phenyl)-benzamide methanesulfonate corresponding to the molecular formula $C_{30}H_{35}N_7SO_4$. It has a relative molecular mass of 589.7 g/mol and the following structure:

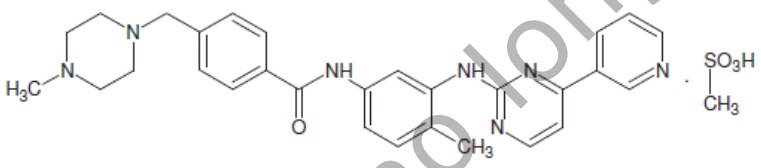

Figure 1: active substance structure

Multiple manufacturers of imatinib mesylate are used by the applicant. A monograph for imatinib mesylate has been published in the European Pharmacopoeia (Ph. Eur.) and both manufacturers have been granted Certificates of Suitability of the European Pharmacopoeia (CEPs), which have been provided within the current Marketing Authorisation Application.

Two polymorphic forms of imatinib mesylate are known. Both manufacturers produce the desired polymorphic form and a test to ensure this is included in the respective specifications.

Manufacture, characterisation and process controls

The relevant information has been assessed by the EDQM before issuing the CEPs.

Specification

The control tests are carried out to comply with the specifications and test methods of the Ph. Eur. monograph. Additional specifications have been set for residual solvents. All additional methods have been adequately validated and described according to ICH Q2. The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

Stability

The proposed re-test periods and the materials of the container closure systems for imatinib mesylate are covered by the respective CEPs.

2.2.3. Finished medicinal product

Film-coated tablets:

Description of the product and Pharmaceutical development

Imatinib 100 mg film-coated tablets are dark yellow to brownish orange round film-coated tablets debossed with "IT" and "1" divided by score line on one side. Each tablet contains 100 mg of imatinib in the form of the mesylate salt.

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. Each tablet contains 400 mg of imatinib in the form of the mesylate salt.

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. Disintegration time and dissolution were considered as most critical properties of the immediate release oral dosage form during the formulation development phase.

The commercial manufacturing process comprises granulation followed by compression and film-coating.

Other than the film-coating mixture, all excipients used in the formulation are compendial, well-known and widely used in this type of dosage form and their quality is compliant with Ph. Eur. standards. The Opadry components are either of compendial quality (polyvinyl alcohol, titanium dioxide, talc, macrogol) or controlled by in-house specifications (colour agents).

The development of Imatinib film coated tablets 100 mg and 400 mg was initially done at one manufacturing site but the process was transferred, during development, to a second manufacturing site which is the proposed commercial site. Bioequivalence was demonstrated between 400 mg tablets manufactured at the initial site with 400 mg reference product tablets. Given that the 100 mg tablets have the same qualitative and quantitative composition as 400 mg tablets, are produced by the same manufacturer, and have similar rapid *in vitro* dissolution profiles at pH 1.2, 4.5 and 6.8, a biowaiver of strengths was deemed acceptable. In order to demonstrate that tablets manufactured at the commercial site are equivalent to the biobatch, a series of *in vitro* dissolution studies was undertaken. The results showed that dissolution profiles of the various tablets were similar across the physiologically-relevant pH range.

The QC dissolution method was developed bearing in mind the high solubility of imatinib mesylate across the physiological pH range (BCS class I). After significant optimisation, the QC dissolution method was shown not to have much discriminatory power in relation to meaningful changes in the manufacturing process. However, due to the high inherent solubility of the active substance, it was deemed to be a suitable method for QC purposes.

Polymorphic form stability was investigated using active substance from both suppliers, as well as in tablets following formulation. Samples were analysed by X-ray powder diffraction (XRPD) following storage for up to 12 months under long term or accelerated conditions (see stability section) and

compared to the diffractograms taken at T_0. It was demonstrated that the tablets contain and no change in the solid state characteristics occur during storage under either condition.

Since the tablets contain score lines, a test of subdivision of tablets has been performed according to Ph. Eur. All results comply with the pharmacopoeial requirements.

The primary packaging is either PVC/PE/PVdC/PE/PVC//Al blisters or OPA/Al/PVC//Al blisters. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of five main steps: granulation, homogenisation of the granules, compression, film-coating and packaging. The process is considered to be a standard manufacturing process.

The manufacturing process has been validated at full scale on three consecutive batches of each strength. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form including description (visual), identity (HPLC, UV), assay (HPLC), uniformity of dosage units (Ph. Eur.), related substances (HPLC), sub-division of tablets (Ph. Eur.), dissolution (HPLC), loss on drying (Ph. Eur.), identity of colorants (colour test) and microbial limits (Ph. Eur.).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results were provided for three production scale batches of each strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from five production scale batches of each strength of finished product from the commercial manufacturer stored for up to 9 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing. Two batches of each strength were stored in PVC/PE/PVdC/PE/PVC//Al blisters and three were stored in OPA/Al/PVC//Al blisters. In addition, results were provided from two pilot scale batches of each strength from the initial manufacturer stored in alu/alu blisters or HDPE bottles for up to 24 months under long term conditions and for up to 6 months under accelerated conditions. Samples were tested for assay, related substances, dissolution, loss on drying, description and microbial limits. The analytical procedures used are stability indicating. No significant changes were observed to any of the measured parameters in any of the studies indicating that the product is stable.

Freeze-testing was also performed at -20 ^{o}C which had no impact on the quality of the product.

Based on available stability data, the proposed shelf-life of 2 years without special storage conditions as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

Hard capsules:

Description of the product and Pharmaceutical development

Imatinib capsules 100 mg are non-transparent orange capsules with "7629" printed in black on the capsule body and "TEVA" on the cap. The content of the capsule is a white to light yellow granulated powder. Each capsule contains 100 mg of imatinib as the mesylate salt.

Imatinib capsules 400 mg are non-transparent orange capsules with "7630" printed in black on the capsule body and "TEVA" on the cap. The content of the capsule is a white to light yellow granulated powder. Each capsule contains 400 mg of imatinib as the mesylate salt.

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

Excipients used in the formulation are all compendial, well-known or widely used for this type of dosage form. Their quality is compliant with Ph. Eur. or in-house standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

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 satisfactory stability. The scale up of the process was achieved by defining optimal process parameters and ranges.

Bioequivalence was established clinically between 400 mg capsules and 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. Only minimal differences in dissolution profiles of different formulations were observed. Such behaviour was expected due to very high solubility of drug substance (> 300 mg/ml), which dissolves rapidly after capsule opening. Since the formulation contains a high amount of active substance, dissolution is not influenced by the excipients. Therefore, dissolution is not a critical quality parameter for this product.

A series of *in vitro* dissolution studies in 0.1 M HCl, pH 4.5 and pH 6.8 was conducted in order to demonstrate the similarity in dissolution rate between the capsules and the reference product. The dissolution profiles of Glivec 400 mg tablets were compared with the biobatch 400 mg capsules. A comparison between Imatinib Teva 100 and 400 mg capsules was also performed. Glivec 100 mg capsules were compared with Imatinib Teva 100 mg capsules. Finally, Glivec 100 mg tablets were compared with Imatinib Teva 100 mg capsules. In all tested dissolution media for each dosage form, rapid and complete dissolution (> 85% in 15 minutes) was observed indicating that they have similar dissolution rates.

Since all requirements for a biowaiver of strengths are in place for the 100 mg capsule (same qualitative and quantitative composition as 400 mg capsules, produced by the same manufacturer, similar rapid in vitro dissolution profiles), no clinical bioavailability study was required.

The primary packaging is PVC/PE/PVdC/PE/PVC//Al blisters and OPA/Al/PVC//Al blisters. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of seven main steps: mixing of intra-granular excipients, roller compaction, screening, milling, homogenisation, encapsulation and packaging. The process is considered to be a standard manufacturing process.

The manufacturing processes have been adequately described and the critical steps have been identified. The different steps of the manufacturing processes are described, together with equipment type and operating parameters.

The validation protocol has been provided which describes how the commercial process will be validated in production scale before commercialisation. The quality of the production batches will be evaluated by in process testing as well as the results of finished product testing. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form including description of capsules and their contents (visual), water content (KF), identity (HPLC, UV), assay (HPLC), uniformity of dosage units (Ph. Eur.), related substances (HPLC), dissolution (HPLC) and microbial limits (Ph. Eur.).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for three production scale batches of each strength of capsule confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from six production scale batches of each strength of imatinib capsule stored for up to 12 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and three batches of each strength were packed in each of primary packaging formats proposed for marketing.

Samples were tested for assay, related substances, dissolution, water content, description and microbial limits. The assay and impurity methods were changed during stability studies and a method comparison report demonstrates that the new method is a suitable replacement. The analytical procedures used are stability indicating. No significant changes to any of the measured parameters were observed under either storage condition and in either packaging format were observed indicating that the capsules are stable.

Freeze-testing was also performed at -20 °C. In addition, one batch per strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Neither freezing nor exposure to light under the conditions investigated has any negative impact on the quality of the product.

Based on available stability data, the proposed shelf-life of 24 months stored below 30 °C as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

Gelatine obtained from bovine sources is used in the product. Valid TSE CEP from the suppliers of the gelatine used in the manufacture is provided. No excipients derived from human origin have been used.

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 clinical use.

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. Recommendations 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 BV 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 the non-clinical aspects

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.

This is in accordance with the relevant guideline and additional non clinical studies were not considered necessary.

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 CHMP'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 meet 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 studies 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 has been sponsored by Ratiopharm GmbH: 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 has been sponsored by Pliva HRVATSKA. d.o.o.: 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

Test and reference products

Study 1 (film-coated tablets)

Test Product: Imatinib 400 mg film coated tablets. Batch number: 345Z-25.

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 400 mg hard capsules. Batch number: 414120/221120/T.

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

CoA for reference product has been submitted.

Populations 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.

One patient 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 analysed but excluded from the statistical analysis.

Forty-two (42) subjects were analysed and forty-one (41) were included in the pharmacokinetic and statistical analysis.

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 14. All subjects were analyzed and were included in the pharmacokinetic and statistical analysis.

Analytical methods

Study 1 (film-coated tablets)

Pre-study validation

The analytical method validation report describes the method validation for the determination of Imatinib and N-Desmethyl Imatinib in human plasma using K2EDTA as anticoagulant. Back-calculated concentrations were determined for Imatinib using least squares regression analysis employing a weighted (1/x) quadratic regression ($y=ax^2+bx+c$). 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 centres 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 dated July 19th, 2010 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 one 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 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 2 (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 (y = ax2 + bx + c) was used to evaluate Imatinib standard concentrations. All calibration points are weighted by the factor 1/c. Back-calculated standard concentrations from the independent calibration curves are provided.

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

In-study validation

Bioanalitycal report dated March 10th, 2011 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 AUC_{0-72}. Other parameters such as T_{max}, AUC_{∞}, $AUC_{0-72/\infty}$, K_{el} and $T_{½el}$ were provided for information purposes only. The natural logarithmic transformation of C_{max}, AUC_{0-72} 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

Table 2. Comparison of Results with Standards for Bioequivalence -

PARAMETER	INTRA-SUBJECT C.V. (%)	GEOMETRIC LSMEANS *		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TEST	REFERENCE		LOWER	UPPER
C_{max}	9.9	1984.9	1978.3	100.34	96.72	104.09
AUC_{0-72}	9.4	34553.0	34853.5	99.14	95.74	102.65

* units are ng/mL for C_{max} and ng·h/mL for AUC_{0-72}

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

A biowaiver applies for the 100 mg dose strength.

Study 2

Table 3. Comparison of Results with Standards for Bioequivalence –

Parameter	TRT	Means			Contrast	Ratio	90% CI		Intra-Sub CV(%)
		Arithmetic(±SD)	(CV%)	Geometric			Lower	Upper	
Based on Measured Data									
AUC_t *(ng*h/mL)*	A	28925.3 (6958.2)	(24)	28224.3	A vs. B	100.66	96.37	- 105.14	8
	B	28508.6 (5400.2)	(19)	28040.2					
AUC_{inf} *(ng*h/mL)*	A	29764.2 (7073.6)	(24)	-	-	-	-	- -	-
	B	29240.7 (5522.3)	(19)						
Cmax *(ng/mL)*	A	1704.5 (338.4)	(20)	1674.3	A vs. B	93.23	89.14	- 97.51	8
	B	1835.0 (396.8)	(22)	1795.9					
Tmax *(h)*	A	4.83 (1.10)	(23)						
	B	3.70 (1.25)	(34)						
Kel *(1/h)*	A	0.0509 (0.0075)	(15)						
	B	0.0520 (0.0073)	(14)						
Thalf *(h)*	A	13.94 (2.24)	(16)						
	B	13.57 (1.89)	(14)						

Based on the statistical analysis the test product is equivalent to the reference with respect to the extent and rate of absorption/exposure. The 90% confidence intervals calculated for $AUC_{(0-72)}$ and C_{max} of Imatinib were inside the normal range of acceptability (80.00 – 125.00).

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 is anticipated.

Conclusions

Based on the submitted bioequivalence studies, both meet the bioequivalence criteria with respect to the rate and extent of absorption of Imatinib.

The results of the bioequivalence studies with the 400 mg formulation can be extrapolated to the 100 mg strengths (film-coated and hard capsules)

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

application.

2.4.3. Post marketing experience

No post-marketing data are available.

2.4.4. Discussion and conclusions on clinical aspects

Based on the submitted bioequivalence studies, both meet the bioequivalence criteria with respect to the rate and extent of absorption of Imatinib.

The results of the bioequivalence studies with the 400 mg formulation can be extrapolated to the 100 mg strengths (film-coated and hard capsules).

2.5. Risk management plan

Safety concerns

Table: Summary of safety concerns	
Important identified risks	Myelosupression Oedema and fluid retention CNS and gastrointestinal haemorrhages Gastrointestinal obstruction, perforation or ulceration Hepatotoxicity Skin rashes and severe cutaneous reactions Hypothyroidism Hypophosphatemia Cardiac failure Acute renal failure Severe respiratory adverse reactions Rhabdomyolysis and myopathy Ovarian haemorrhage and haemorrhagic ovarian cyst Tumour lysis syndrome Growth retardation in children Interaction with strong CYP3A4 inhibitors Interaction with strong CYP3A4 inducers Interaction with drugs eliminated by CYP3A4
Important potential risks	Second malignancies in survivors Disseminated intravascular coagulation Hypoglycaemia Suicidality Tolerability during pregnancy and pregnancy outcomes Interaction with drugs eliminated by CYP2C9, CYP2C19 AND CYP2D6
Missing information	Paediatric patients: long term follow up Paediatric patients below 2 years of age Use in patients with renal impairment Use in patients with hepatic impairment

Pharmacovigilance plan

Routine pharmacovigilance activities are sufficient to identify and characterise the risks of the product.

The MAH is strongly recommended to contribute and participate in the planned or ongoing studies performed by the MAH of the originator product since it is important (especially for long term safety studies) that all available prospective data are collected in one study.

Routine pharmacovigilance remains sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
IMPORTANT IDENTIFIED RISKS		
Myelosupression	Text in SmPC The risk is listed in Section 4.2, Section 4.4 and Section 4.8, Section 4.9 and Section 5.3 Prescription only medicine	None proposed
Oedema and fluid retention	Text in SmPC The risk is listed in Section 4.4, Section 4.8 and Section 4.9 Prescription only medicine	None proposed
CNS and gastrointestinal haemorrhages	Text in SmPC Risk listed in Section 4.4 and Section 4.8 Prescription only medicine	None proposed
Gastrointestinal obstruction, perforation or ulceration	Text in SmPC The risk is listed in Section 4.8. Prescription only medicine	None proposed
Hepatotoxicity	Text in SmPC The risk is listed in Section 4.2, Section 4.4, Section 4.8 and Section 5.2. Prescription only medicine	None proposed
Skin rashes and severe cutaneous reactions	Text in SmPC The risk is listed in Section 4.8 Prescription only medicine	None proposed
Hypothyroidism	Text in SmPC The risk is listed in Section 4.4 and Section 4.5. Prescription only medicine	None proposed
Hypophosphatemia	Text in SmPC The risk is listed in Section 4.8.	None proposed
Cardiac failure	Text in SmPC The risk is listed in Section 4.4 and Section 4.8 Prescription only medicine	None proposed
Acute renal failure	Text in SmPC The risk is listed in Section 4.2, Section 4.4, Section 4.8 and Section 5.2. Prescription only medicine	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Severe respiratory adverse reactions	Text in SmPC The risk is listed in Section 4.8. Prescription only medicine	None proposed
Rhabdomyolysis and myopathy	Text in SmPC Risk listed in Section 4.8 Prescription only medicine	None proposed
Ovarian haemorrhage and haemorrhagic ovarian cyst	Text in SmPC Risk listed in Section 4.8 Prescription only medicine	None proposed
Tumour lysis syndrome	Text in SmPC Risk listed in Section 4.4 and Section 4.8 Prescription only medicine	None proposed
Growth retardation in children	Text in SmPC Risk listed in Section 4.2, Section 4.4, Section 4.8. Prescription only medicine	None proposed
Interaction with strong CYP3A4 inhibitors	Text in SmPC Risk listed in Section 4.5. Prescription only medicine	None proposed
Interaction with strong CYP3A4 inducers	Text in SmPC Risk listed in Section 4.4 and Section 4.5 Prescription only medicine	None proposed
Interaction with drugs eliminated by CYP3A4	Text in SmPC Risk listed in Section 4.4 and Section 4.5 Prescription only medicine	None proposed
IMPORTANT POTENTIAL RISKS		
Second malignancies in survivors	Text in SmPC Risk listed in Section 5.3 Prescription only medicine	None proposed
Disseminated intravascular coagulation	No risk minimisation activities are proposed. There is a lack of conclusive data indicating causal relationship at this time. Should PV activities uncover additional data, the risk will be communicated through the labelling and additional risk minimisation activities may be proposed if necessary. Prescription only medicine	None proposed
Hypoglycaemia	No risk minimisation activities are proposed.There is a lack of conclusive data indicating causal relationship at this time. Should PV activities uncover additional data, the risk will be communicated through the labelling and additional risk minimisation activities may be proposed if necessary. Prescription only medicine	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Suicidality	No risk minimisation activities are proposed. There is a lack of conclusive data indicating causal relationship at this time. Should PV activities uncover additional data, the risk will be communicated through the labelling and additional risk minimisation activities may be proposed if necessary. Prescription only medicine	None proposed
Tolerability during pregnancy and pregnancy outcomes	Text in SmPC Risk listed in Section 4.6 and Section 5.3 Prescription only medicine	None proposed
Interaction with drugs eliminated by CYP2C9, CYP2C19 AND CYP2D6	Text in SmPC Risk listed in Section 4.5 Prescription only medicine	None proposed
MISSING INFORMATION		
Paediatric patients: long term follow up	Text in SmPC Risk listed in Section 4.2, Section 4.4, Section 4.8 and Section 5.3 Prescription only medicine	None proposed
Paediatric patients below 2 years of age	Text in SmPC Risk listed in Section 4.2 Prescription only medicine	None proposed
Use in patients with renal impairment	Text in SmPC Risk listed in Section 4.2, Section 4.4, Section 4.8 and Section 5.2 Prescription only medicine	None proposed
Use in patients with hepatic impairment	Text in SmPC Risk listed in Section 4.2, Section 4.4, Section 4.8 and Section 5.2 Prescription only medicine	None proposed

The PRAC, 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.

Conclusion

The CHMP and PRAC considered that the risk management plan version 2.3, dated 10 July 2017, is acceptable.

2.6. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Product information

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

The applicant submitted a duplicate application of the product Imatinib Teva. Since a successfully user consultation for Imatinib Teva was performed it is considered an acceptable justification for not performing user consultation for Imatinib Teva B.V.

3. Benefit-risk balance

This application concerns a duplicate version of imatinib Teva film-coated tablets and hard capsules (EMEA/H/C/002585). 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 BV 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 is of the opinion that Imatinib Teva B.V. is not similar to Tasigna (nilotinib), Bosulif (bosutinib), Iclusig (ponatinib), Xaluprine (6-mercaptopurine monohydrate), Atriance (nelaranibe), Blincyto (blinatumomab), Vidaza (azacitidine), Revlimid (lenalidomide) and Besponsa (inotuzumab ozogamicin)
within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1

Outcome

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 B.V. is favourable in the following indication:

Imatinib Teva B.V. 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.
- Adult and paediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) integrated with chemotherapy.
- Adult patients with relapsed or refractory Ph+ ALL as monotherapy.
- Adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements.
- Adult patients with advanced hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL) with FIP1L1-PDGFRα rearrangement.

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

Imatinib Teva B.V. is indicated for

- The treatment of adult patients with Kit (CD 117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST).
- The adjuvant treatment of adult patients who are at significant risk of relapse following resection of Kit (CD117)-positive GIST. Patients who have a low or very low risk of recurrence should not receive adjuvant treatment.
- The treatment of adult patients with unresectable dermatofibrosarcoma protuberans (DFSP) and adult patients with recurrent and/or metastatic DFSP who are not eligible for surgery.

In adult and paediatric patients, the effectiveness of imatinib is based on overall haematological and cytogenetic response rates and progression-free survival in CML, on haematological and cytogenetic response rates in Ph+ ALL, MDS/MPD, on haematological response rates in HES/CEL and on objective response rates in adult patients with unresectable and/or metastatic GIST and DFSP and on recurrence-free survival in adjuvant GIST. The experience with imatinib in patients with MDS/MPD associated with PDGFR gene re-arrangements is very limited (see section 5.1). There are no controlled trials demonstrating a clinical benefit or increased survival for these diseases.

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).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

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

Risk Management Plan (RMP)

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

An updated RMP should be submitted:

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