20 March 2014
EMA/284461/2014
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Imatinib Actavis

International non-proprietary name: Imatinib

Procedure No.: EMEA/H/C/002594/X/0003

Note

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

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Table of contents

List of abbreviations

AGEP	acute generalised exanthematous pustulosis
AGP	alpha-acid glycoprotein
ALL	acute lymphoblastic leukaemia
Al	aluminium
ANC	absolute neutrophil count
ANOVA	analysis of variance
ASMF	active substance master file
AST	aspartate aminotransferase
AUC_{0-t}	area under the plasma concentration curve from administration to last observed concentration at time t.
$AUC_{0-\infty}$	area under the plasma concentration curve extrapolated to infinite time
Bcr-Abl	Philadelphia chromosome
CEL	chronic eosinophilic leukaemia
CHMP	Committee for Medicinal Products for Human Use
C_{max}	maximum plasma concentration
CML	chronic myeloid leukaemia
CNS	central nervous system
DE	Germany
DFSP	dermatofibrosarcoma protuberans
EC	European Commission
EIAED	enzyme-inducing anti-epileptic drug
EMA	European Medicines Agency
ERA	environmental risk assessment
EURD	European Union reference dates
GCP	good clinical practice
GIST	gastrointestinal stromal tumour
GLM	general linear models
GLP	good laboratory practice
HES	hypereosinophilic syndrome
HMG CoA	3-hydroxy-3-methylglutaryl coenzyme A
HPLC	high performance liquid chromatography
ICH	International Conference on Harmonisation (of technical requirements for registration of pharmaceuticals for human use)
ISR	incurred sample reanalysis
IULN or ULN	institutional upper limit of normal
IPC	in-process control
K_{el}	elimination constant
MAH	marketing authorisation holder
MDS	myelodysplastic
MPD	myeloproliferative disease
MS	mass spectrometry
NOEL	no overall effect level
PDGFR	platelet-derived growth factor receptor
Ph+	Philadelphia chromosome (Bcr-Abl) positive
Ph. Eur.	European Pharmacopoeia
PK	pharmacokinetics
PRAC	Pharmacovigilence Risk Assessment Committee
PSUR	periodic safety update report
PVC	polyvinylchloride
PVDC	polyvinylidene chloride
QC	quality control
RH	relative humidity
RMP	risk management plan
SmPC	summary of product characteristics
$T_{½el}$	elimination half-life
TLS	tumour lysis syndrome
T_{max}	time until C_{max} is reached
UV	ultraviolet
WBC	white blood cell

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Actavis Group PTC ehf submitted on 5 June 2013 an extension application for Marketing Authorisation to the European Medicines Agency (EMA) for Imatinib Actavis 400 mg hard capsules, through the centralised procedure falling within the Article 19 (1) and Annex I (point 2 indent c) of Regulation (EC) No 1234/2008.

Actavis Group PTC ehf is already the Marketing Authorisation Holder for Imatinib Actavis 50 and 100 mg hard capsules and 100 and 400 mg film-coated tablets EU/1/13/825/001-019.

The applicant applied for the following indication:

- paediatric patients with newly diagnosed Philadelphia chromosome (Bcr-Abl) positive (Ph+) chronic myeloid leukaemia (CML) for whom bone marrow transplantation is not considered as the first line of treatment.
- paediatric patients with Ph+ CML in chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis.
- adult patients with Ph+ CML in blast crisis.
- adult patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) integrated with chemotherapy.
- adult patients with relapsed or refractory Ph+ ALL as monotherapy.
- adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements.
- adult patients with advanced hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL) with FIP1L1-PDGFRα rearrangement.

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

Imatinib Actavis is indicated for:

- 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 DFSP. 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:

The application submitted is composed of administrative information, complete quality data and a clinical bioequivalence study with the reference medicinal product Glivec 400 mg film-coated tablets, marketing authorization number EU/1/01/198/010.

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 Tasigna, Sprycel, Vidaza, Evoltra, Atriance, Xaluprine, Bosulif, Iclusig and Revlimid.

Licensing status

Imatinib Actavis has been given a Marketing Authorisation in the European Union on 17 April 2013.

1.2. Manufacturers

Manufacturer(s) responsible for batch release

S.C. Sindan-Pharma S.R.L.
11th Ion Mihalache Ave
The 1st District
Bucharest 011171
Romania

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Reynir Arngrímsson Co-Rapporteur: N/A

- The application was received by the EMA on 5 June 2013.
- The procedure started on 24 July 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 14 October 2013.
- During the PRAC meeting on 07 November 2013, the PRAC adopted an RMP Advice.
- During the meeting on 21 November 2013, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 21 November 2013.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 19 December 2013.
- The Rapporteur circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 17 January 2014.
- During the PRAC meeting on 06 February 2014, the PRAC adopted an RMP Advice.
- During the CHMP meeting on 20 February 2014, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 24 February 2014.

- The Rapporteur circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 05 March 2014.
- During the meeting on 20 March 2014, 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 a report on similarity of Imatinib Actavis with Tasigna, Sprycel, Vidaza, Evoltra, Atriance, Xaluprine, Bosulif, Iclusig and Revlimid on 19 September 2013.

2. Scientific discussion

2.1. Introduction

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

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.

Imatinib Actavis is currently 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.

This is a line extension application for a new 400 mg strength of Imatinib Actavis hard capsules to add to those already approved. In addition, the applicant has extended the set of indications to those for the reference product, Glivec. The proposed indication for Imatinib Actavis 400 mg hard capsules is for treatment of:

- paediatric patients with newly diagnosed Philadelphia chromosome (Bcr-Abl) positive (Ph+) chronic myeloid leukaemia (CML) for whom bone marrow transplantation is not considered as the first line of treatment.
- paediatric patients with Ph+ CML in chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis.
- adult patients with Ph+ CML in blast crisis.

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

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

Imatinib Actavis is indicated for

- 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 DFSP. 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 product is presented as hard capsules containing 400 mg of imatinib as active substance as the mesylate salt.

Other ingredients are microcrystalline cellulose, copovidone, crospovidone, sodium stearyl fumarate, hydrophobic colloidal silica, anhydrous colloidal silica, hypromellose, titanium dioxide (E171), iron oxide yellow (E172), iron oxide red (E172) iron oxide black (E172), shellac glaze-45%, black iron oxide (E172), propylene glycol and ammonium hydroxide 28%.

The product is available in Al/PVDC-PVC blisters, in packs of 10, 30, 60, or 90 capsules.

2.2.2. Active Substance

Imatinib Actavis 400 mg hard capsules contain the same active substance as that used to manufacture the already authorised presentations. The active substance is sourced from the same manufacturer, manufactured with the same process and released in accordance with the same active substance specifications. The applicant referred to the active substance master file of the already authorised hard capsules for Imatinib Actavis and no new information on the active substance has been provided.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The aim of the pharmaceutical development was to develop an immediate release 400 mg strength of the hard capsule presentation, bioequivalent to the reference product, Glivec 400 mg film-coated tablets. Several polymorphic forms of Imatinib mesylate are known. The amorphous form of Imatinib mesylate employed in the manufacture of the 50 and 100 mg hard capsules was used to develop the new strength too.

The Imatinib Actavis 400 mg hard capsule formulation was based on experience accumulated during the development and manufacturing of 50 mg and 100 mg strengths and contains the same excipients. However, the quantitative composition is not proportional to the lower strengths as these had to be optimised for the relatively lower capacity of size 00 capsule and the flow properties of the final blend for capsule filling. Thus, the overall excipient content and the granulate particle size were reduced and additional extra-granular microcrystalline cellulose was added to increase bulk density.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

Bioequivalence was demonstrated by an in vivo single dose crossover PK study (study IAI-P1-740) performed under fed conditions as per SmPC section 4.2. The formulation used during the BE study is the same that intended to be marketed.

The dissolution profile of Imatinib Actavis 400 mg hard capsules was compared with that of the Glivec 400 mg film coated tablet reference product. Comparative in vitro dissolution studies (Ph. Eur. 5.17.1) over the pH range 1.2-6.8 revealed great differences in dissolution profiles with Imatinib Actavis hard capsules dissolving more slowly. However, it is noted that the dissolution mechanism for capsules is different than for tablets since the capsule requires time to hydrate and disintegrate before releasing the active substance, and so the two dosage forms cannot therefore be directly compared.

The proposed dissolution method used for quality control has been demonstrated to be discriminatory for the 50 and 100 mg hard capsules by comparing dissolution profiles between one intentionally mis-manufactured batch and the batch used for the bioequivalence study. Given that dissolution profile is primarily associated with the hard capsule rupture, and the clinical bioequivalence data, it was concluded that the suitability of the dissolution method, already approved for the lower strength hard capsules, could be extrapolated to the 400 mg strength.

The primary packaging is Al/PVDC-PVC blisters. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Adventitious agents

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

Manufacture of the product

The manufacturing process is a standard process for this type of product, but differs slightly from the 50 and 100 mg strengths as the qualitative composition is different. It consists of five main steps: mixing of active substance with granular excipients, granulation by compaction, mixing of granules with extra-granular excipients, filling of the capsules, and packaging. There are no critical steps; it is a simple

dry granulation and encapsulation process. The proposed IPCs (e.g. appearance and content uniformity of blend prior to filling) are acceptable considering the pharmaceutical form.

The applicant commits to formal validation of the manufacturing process for the 400 mg hard capsules with the first three commercial batches. The respective validation protocol was provided and is considered acceptable, given the standard manufacturing process.

Product specification

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), 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 ICH Q3B guideline. Appropriate limits for the two 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).

Batch analysis results are provided on two commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data of two batches of finished product stored for up to 12 months under long term conditions at 25 °C ± 2 °C / 60% ± 5% RH, for up to 12 months under intermediate conditions at 30 °C ± 2 °C / 65% ± 5% RH and for up to 6 months under accelerated conditions at 40 °C ± 2 °C / 75% ± 5% RH according to ICH guidance were provided. The batches of finished product are representative of those proposed for marketing and were packed in the primary packaging proposed for marketing. Samples were tested for appearance of capsule and content, assay, water content, dissolution, related substances, and microbiological contamination. The analytical procedures used are stability indicating.

In addition one batch was exposed to light as defined in the ICH guideline on Photostability Testing of New Drug Substances and Products. The finished product showed no signs of photo-induced degradation.

The drug product is generally stable under long-term conditions in conditions in the PVC-PVDC/Al blisters. The only trends observable are a slight decrease in assay, combined with an increase of total impurities (<0.05 to 0.22%). Levels of the genotoxic impurities remained constant (around 6 and 3 ppm, respectively). Dissolution also remains constant over time. The 400 mg strength shows improved stability as compared to the 50 mg and 100 mg counterparts and so the extra storage condition “Do not store above 25°C. Store in the original package in order to protect from moisture” is not strictly necessary. However, in order to stay harmonized with the other available hard capsule strengths and not to confuse patients when switching from one strength to another, the storage condition is accepted.

Based on the overall results the shelf-life and storage conditions as stated in the SmPC are acceptable. The stability studies will continue up to 36 months under long term conditions and up to 12 months under intermediate conditions. Furthermore, the first 3 commercial batches of Imatinib Actavis 400 mg hard capsules will be included in the stability study and a further commercial batch included yearly thereafter.

2.2.4. Discussion on chemical, pharmaceutical and biological 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.

2.2.6. Recommendation(s) for future quality development

N/A.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, justifying 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.

The CHMP considers that the non-clinical overview is based on up-to-date and adequate scientific literature. It is agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment (ERA) was submitted. This was justified by the applicant as the introduction of Imatinib Actavis is unlikely to result in any significant increase in the combined sales volumes for all imatinib containing products.

2.3.3. Discussion and conclusion on non-clinical aspects

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

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

2.4. Clinical aspects

2.4.1. Introduction

This is an extension application for an extension to the Marketing Authorisation to introduce Imatinib Actavis 400 mg hard capsules. To support the application, the applicant submitted one bioequivalence study with cross-over design under fed conditions. This study was a pivotal study for the assessment.

The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of imatinib based on published literature. The SmPC is in line with the SmPC of the reference product with the exception of the information related to the indications protected by market exclusivity at the time of the Marketing authorisation application.

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

GCP

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

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

- Tabular overview of clinical studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Produc (s); Dosage Regimen; Route of Administrat	Number of Subjects	Healthy Subjects or Diagnosis of patients	Duration Treatment	Study status; Type of Report
BE	Study # IAI-P1-740	Algorithme Pharma Inc, Canada	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 400 mg oral dose administration under fed conditions.	Crossover Fed state randomized, single dose, laboratory-blinded, 2-period, 2-sequence	Imatinib capsule 400 mg single dose oral	23	Healthy subjects	Single dose	Complete; Full

2.4.2. Pharmacokinetics

Study IAI-P1-740: Single Dose Crossover, fed state, laboratory blinded, 2-period, 2-sequence study on Imatinib 400 mg Capsules in healthy volunteers.

Methods

Study design

The bioequivalence study was a single centre, randomised, single dose, laboratory-blinded, 2-period, 2-sequence, crossover bioequivalence study comparing single oral 1 x 400 mg dose of two different formulations of imatinib, Imatinib 400 mg hard capsules (test) and Glivec 400 mg film-coated tablet (reference) under fed conditions.

Test and reference products

Imatinib 400 mg hard capsules by Actavis Group PTC efh., Iceland (batch no. EJ11002B, retest date 03 2012, assay of imatinib 409.85 m/capsule) has been compared to Glivec 400 mg film-coated tablets (batch no. S0016, from the DE market, exp. date 08 2014, assay of imatinib 388.15 mg/tablet). The test product is identical to the formulation intended to be marketed.

Population(s) studied

Twenty-four (24) healthy adult male subjects were planned for inclusion but 23 were enrolled and randomised. All of the 23 subjects who were included in the study completed both periods and were analysed and included in the pharmacokinetic and statistical analysis.

Analytical methods

A reversed-phase HPLC method with MS/MS detection to determine Imatinib concentrations in K2EDTA human plasma was successfully validated pre-study and within study over a theoretical concentration range of 10.0 ng/ml to 4000.0 ng/ml. The internal standard used was Imatinib-D8. The quality control (QC) concentrations of Imatinib were 10.0 ng/ml, 30.0 ng/ml, 750.0 ng/ml and 3000.0 ng/ml.

In order to have QC concentration levels that reflect the majority of study sample concentrations, an additional QC level (1200.0 ng/ml) was prepared and incorporated into study sample batches. A total of 920 samples were analysed and 2 samples (0.2% of total analysed samples) were repeated due to sample lost in processing. For incurred sample reanalysis (ISR) 92 samples were run and the results were acceptable. Long term stability at -20°C nominal was proven for a period that spanned the time from first study sample collection to completion of ISR analysis.

Pharmacokinetic variables

The primary pharmacokinetic parameters for this study were AUC0-t and Cmax. The secondary pharmacokinetic parameters AUC0-∞, AUC0-t/AUC0-∞, Tmax, T1/2el and Kel were provided for informational purposes only. Non-compartmental approach was used to assess the pharmacokinetic parameters. Standard methods were used.

The statistical and pharmacokinetic analyses were generated using Kinetic, version 9.01, an application developed at Algorithme Pharma and SAS® version 9 (GLM procedure).

Statistical methods

A parametric ANOVA was performed on the ln-transformed Cmax, AUC0-t and AUC0-∞. The ANOVA model included sequence, period, treatment and subject (nested within sequence) as fixed effects. The test to reference ratio of geometric LSmeans with corresponding two-sided 90% confidence interval based on the ln-transformed Cmax, AUC0-t and AUC0-∞ data were calculated. The parameter Tmax was analyzed using a non-parametric approach. The statistical analyses performed in this study are those that were initially specified in the clinical study protocol.

Criteria for conclusion of bioequivalence:

Bioequivalence is to be concluded 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 Cmax and AUC0-t were all to be within the 80.00 to 125.00% range.

Results

Table 1: **Pharmacokinetic parameters for imatinib (non-transformed values)**

Pharmacokinetic parameter	Test		Reference	
	arithmetic mean	CV%	arithmetic mean	CV%
$AUC_{(0-t)}$ (ng·h/mL)	34065.2	26.9	35122.9	22.8
$AUC_{(0-\infty)}$ (ng·h/mL)	35047.8	27.0	36086.8	22.6
C_{max} (ng/mL)	1925.4	29.3	2036.2	26.2
T_{max}* (hours)	5.00	(2.67-8.00)	3.50	(2.00-8.00)

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)

Table 2: Statistical analysis for imatinib (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
$AUC_{(0-t)}$	96.44	92.70-100.33	7.8
C_{max}	94.12	89.50-98.97	9.9

*estimated from the Residual Mean Squares

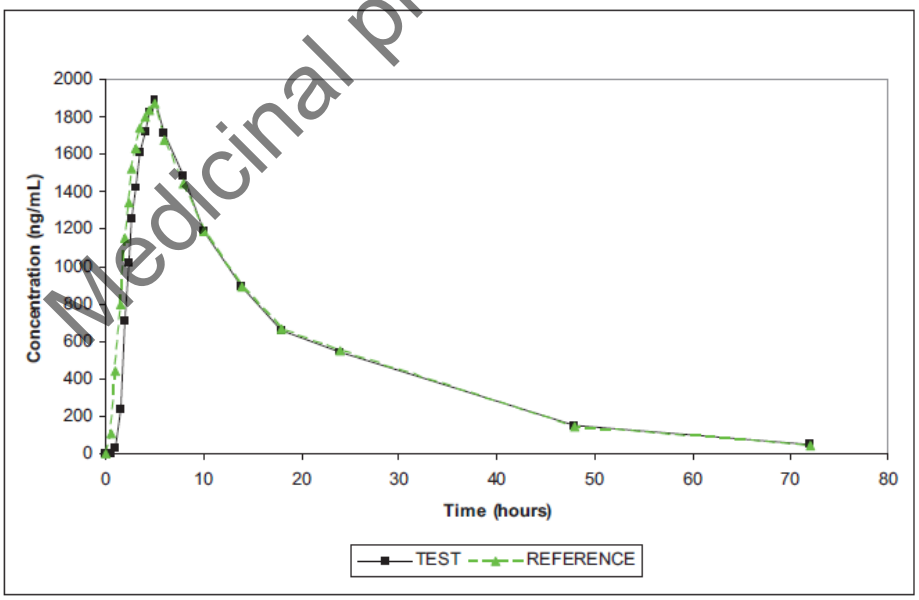

Figure 1: Linear profile of the mean imatinib plasma concentrations versus time in healthy adult male subjects (n=23).

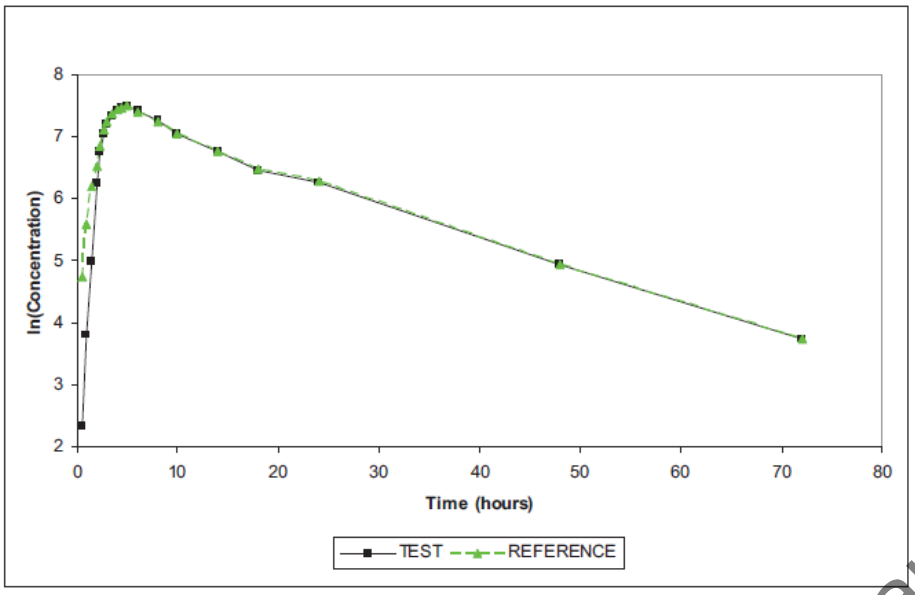

Figure 2: Logarithmic profile of the mean imatinib plasma concentrations versus time in healthy adult subjects (n=23).

The results presented herein show that the criteria used to assess the comparative bioavailability between the Test and the Reference formulations were all fulfilled. Therefore, the Test formulation (Imatinib 400 mg hard capsule, Sindan-Pharma SRL, Romania for Actavis Group PTC ehf., Iceland) is judged to be bioequivalent to the Reference formulation (Glivec 400 mg film-coated tablets, Novartis Pharma GmbH, Germany) under fed conditions.

Dissolution profiles

Dissolution profiles were performed on Imatinib 400 mg hard capsules, batch EJ11002B and reference product Glivec 400 mg film coated tablets batch S0016 purchased from DE market in different pH media (pH 1.2, 2.0, 4.5 and 6.8) and paddle speed of 150 rpm. Dissolution medium (1000 ml) was prepared according to 5.17.1 Section: Recommendations on dissolution testing of European Pharmacopea, Ed 7.

Analysis of the results obtained for *in vitro* dissolution testing of Imatinib 400 mg hard capsules, batch EJ11002B vs. Glivec 400 mg film-coated tablets, batch S0016 have shown that the drug products are not similar (f2<50), when tested at 150 rpm, in all dissolution media.

Although results obtained for similarity factor between Imatinib 400 mg hard capsules and reference product Glivec 400 mg film-coated tablets are not satisfactory, *in vivo* bioequivalence study results have shown that Imatinib 400 mg hard capsules is bioequivalent when compared to Glivec 400 mg film coated tablets.

Safety data

Eight (8) (34.8%) of the 23 subjects included in this study experienced a total of 22 adverse events. Five (5) subjects (21.7%) reported 10 adverse events after the single dose administration of the test product and 6 subjects (26.1%) reported 12 adverse events after the single dose administration of the reference product. All adverse events were mild except for one severe adverse event. 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.

Pharmacokinetic conclusion

Based on the presented bioequivalence study Imatinib Actavis 400 mg hard capsules are considered bioequivalent with Glivec 400 mg film-coated tablets under fed conditions.

2.4.3. Pharmacodynamics

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

2.4.4. Discussion on clinical aspects

In support of the application, the applicant has submitted one (1) bioequivalence study. Statement of GCP compliance and compliance with applicable principles of GLP was provided.

The study was a single centre, randomised, single dose, laboratory-blinded, 2-period, 2-sequence, crossover bioequivalence study comparing single oral 1 x 400 mg dose of two different formulations of imatinib, Imatinib 400 mg hard capsules (test) and Glivec 400 mg film-coated tablet (reference) in 23 healthy adult male subjects under fed conditions. After a supervised overnight fast of at least 10 hours, subjects received a standardised high-fat, high-calorie meal 30 minutes before drug administration. The composition of the meal was according to the Guideline on the Investigation of Bioequivalence. The study was conducted under standardised conditions. The sampling points, overall sampling time as well as wash-out period of 14 calendar days were adequate. Imatinib was measured in human plasma using a validated reversed-phase HPLC method with MS/MS detection. The pharmacokinetic and statistical methods applied were adequate. 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%. Bioequivalence of the two formulations was demonstrated. The *in vitro* dissolution tests of the biobatches do not reflect bioequivalence as demonstrated *in vivo*. The possible reasons for the discrepancy have not been addressed and justified (refer to section 5.3). The drugs were generally safe and well tolerated by the subjects included in the study.

2.4.5. Conclusions on the clinical aspects

The application contains an adequate review of published clinical data and the bioequivalence has been shown between Imatinib Actavis 400 mg hard capsules and Glivec 400 mg film-coated tablets under fed conditions. Approval could be recommended from the clinical point of view provided that adequate response is given to the other concern in Section 5.3.

2.5. Pharmacovigilance

Detailed description of the pharmacovigilance system

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

2.6. Risk Management Plan

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

The RMP is acceptable.

No new risks have been identified for the generic products that are not recognised for the reference product and there are no outstanding issues.

PRAC Advice

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

- **Safety concerns**

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 Interaction with acetaminophen/paracetamol
Missing information	Paediatric patients: long term follow up Paediatric patients below 2 years of age Renal impairment Hepatic impairment Elderly patients

Having considered the data in the safety specification, the PRAC agrees that the safety concerns listed by the Applicant are appropriate

- **Pharmacovigilance plans**

Actavis has no on-going or planned additional pharmacovigilance studies/activities in the Pharmacovigilance Plan.

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

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

- **Risk minimisation measures**

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Myelosuppression	Proposed text in SmPC Warning in section 4.2 *Haematological adverse reactions* *Dose reduction or treatment interruption for severe neutropenia and thrombocytopenia are recommended as indicated in the table below.*	

HES/CEL (starting dose 100 mg)	ANC < 1.0 x 10^9/l and/or platelets < 50 x 10^9/l	1.Stop imatinib until ANC ≥ 1.5 x 10^9/l and platelets ≥ 75 x 10^9/l. 2.Resume treatment with imatinib at previous dose (i.e. before severe adverse reaction).
Chronic phase CML and MDS/MPD (starting dose 400 mg) HES/CEL (at dose 400 mg)	ANC < 1.0 x 10^9/l and/or platelets < 50 x 10^9/l	1.Stop imatinib until ANC ≥ 1.5 x 109/l and platelets ≥ 75 x 109/l. 2.Resume treatment with imatinib at previous dose (i.e. before severe adverse reaction). 3.In the event of recurrence of ANC < 1.0 x 109/l and/or platelets < 50 x 109/l, repeat step 1 and resume imatinib at reduced dose of 300 mg.
Paediatric chronic phase CML (at dose 340 mg/m^2)	ANC < 1.0 x 10^9/l and/or platelets < 50 x 10^9/l	1. Stop imatinib until ANC ≥ 1.5 x 10^9/l and platelets ≥ 75 x 10^9/l. 2. Resume treatment with imatinib at previous dose (i.e. before severe adverse reaction). 3. In the event of recurrence of ANC < 1.0 x 10^9/l and/or platelets < 50 x 10^9/l, repeat step 1 and resume imatinib at reduced dose of 260 mg/m^2.
Accelerated phase CML and blast crisis and Ph+ ALL (starting dose 600 mg)	[a]ANC < 0.5 x 10^9/l and/or platelets < 10 x 10^9/l	1. Check whether cytopenia is related to leukaemia (marrow aspirate or biopsy). 2. If cytopenia is unrelated to leukaemia, reduce dose of imatinib to 400 mg. 3. If cytopenia persists for 2 weeks, reduce further to 300 mg. 4. If cytopenia persists for 4 weeks and is still unrelated to leukaemia, stop imatinib until ANC ≥ 1 x 10^9/l and platelets ≥ 20 x 10^9/l, then resume treatment at 300 mg.
Paediatric accelerated phase CML and blast crisis (starting dose 340 mg/m^2)	[a]ANC < 0.5 x 10^9/l and/or platelets < 10 x 10^9/l	1. Check whether cytopenia is related to leukaemia (marrow aspirate or biopsy). 2. If cytopenia is unrelated to leukaemia, reduce dose of imatinib to 260 mg/m^2. 3. If cytopenia persists for 2 weeks, reduce further to 200 mg/m^2. 4. If cytopenia persists for 4 weeks and is still unrelated to leukaemia, stop imatinib until ANC ≥ 1 x 10^9/l and platelets ≥ 20 x 10^9/l, then resume treatment at 200 mg/m^2.
DFSP (at dose 800 mg)	ANC < 1.0 x 10^9/l and/or platelets < 50 x 10^9/l	1. Stop imatinib until ANC ≥ 1.5 x 10^9/l and platelets ≥ 75 x 10^9/l. 2. Resume treatment with imatinib at 600 mg. 3.In the event of recurrence of ANC < 1.0 x 10^9/l and/or platelets < 50 x 10^9/l, repeat step 1 and resume imatinib at reduced dose of 400 mg.
ANC = absolute neutrophil count [a] occurring after at least 1 month of treatment		

Warning in section 4.4
Laboratory tests
Complete blood counts must be performed regularly during therapy with imatinib. Treatment of CML patients with imatinib has been associated with neutropenia or thrombocytopenia. However, the occurrence of these cytopenias is likely to be related to the stage of the disease being treated and they were more frequent in patients with accelerated phase CML or blast crisis as compared to patients with chronic phase CML. Treatment with imatinib may be interrupted or the dose may be reduced, as recommended in section 4.2.

Warning in section 4.5
In Ph+ ALL patients, there is clinical experience of co-administering imatinib with chemotherapy (see section 5.1), but drug-drug interactions between imatinib and chemotherapy regimens are not well characterised. Imatinib adverse events, i.e. hepatotoxicity, myelosuppression or others may increase and it has been reported that concomitant use with L-asparaginase could be associated with increased hepatotoxicity (see section 4.8). Therefore, the use of imatinib in combination requires special precaution.

Listed in section 4.8
The adverse reactions were similar in all indications, with two exceptions. There was more

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	myelosuppression seen in CML patients than in GIST, which is probably due to the underlying disease. **Adverse reactions in clinical studies** Blood and lymphatic system disorders: *Very common: Neutropenia, thrombocytopenia, anaemia* *Common: Pancytopenia, febrile neutropenia* *Uncommon: Lymphopenia, bone marrow depression* *Rare: Haemolytic anaemia* **Laboratory test abnormalities** *Haematology* *In CML, cytopenias, particularly neutropenia and thrombocytopenia, have been a consistent finding in all studies, with the suggestion of a higher frequency at high doses ≥ 750 mg (phase I study). However, the occurrence of cytopenias was also clearly dependent on the stage of the disease, the frequency of grade 3 or 4 neutropenias (ANC < 1.0 x 109/l) and thrombocytopenias (platelet count < 50 x 109/l) being between 4 and 6 times higher in blast crisis and accelerated phase (59–64% and 44–63% for neutropenia and thrombocytopenia, respectively) as compared to newly diagnosed patients in chronic phase CML (16.7% neutropenia and 8.9% thrombocytopenia). In newly diagnosed chronic phase CML grade 4 neutropenia (ANC < 0.5 x 109/l) and thrombocytopenia (platelet count < 10 x 109/l) were observed in 3.6% and < 1% of patients, respectively. The median duration of the neutropenic and thrombocytopenic episodes usually ranged from 2 to 3 weeks, and from 3 to 4 weeks, respectively. These events can usually be managed with either a reduction of the dose or interruptions of treatment with imatinib, but can in rare cases lead to permanent discontinuation of treatment. In paediatric CML patients the most frequent toxicities observed were grade 3 or 4 cytopenias involving neutropenia, thrombocytopenia and anaemia. These generally occur within the first several months of therapy.* *In the study in patients with unresectable and/or metastatic GIST, grade 3 and 4 anaemia was reported in 5.4% and 0.7% of patients, respectively, and may have been related to gastrointestinal or intra-tumoural bleeding in at least some of these patients. Grade 3 and 4 neutropenia was seen in 7.5% and 2.7% of patients, respectively, and grade 3 thrombocytopenia in 0.7% of patients. No patient developed grade 4 thrombocytopenia. The decreases in white blood cell (WBC) and neutrophil counts occurred mainly during the first six weeks of therapy, with values remaining relatively stable thereafter.* Warning in section 4.9 *Adult population* *1200 to 1600 mg (duration varying between 1 to 10 days): thrombocytopenia, pancytopenia* Warning in section 5.3 *Multiple dose toxicity studies revealed mild to moderate haematological changes in rats, dogs and monkeys, accompanied by bone marrow changes in rats and dogs.* Other routine risk minimisation measures *Therapy should be initiated by a physician experienced in the treatment of patients with haematological malignancies and malignant sarcomas, as appropriate.*	
Oedema and fluid retention	Proposed text in SmPC Warning in section 4.4 Fluid retention *Occurrences of severe fluid retention (pleural effusion, oedema, pulmonary oedema, ascites, superficial oedema) have been reported in approximately 2.5% of newly diagnosed CML patients taking imatinib. Therefore, it is highly recommended that patients be weighed regularly. An unexpected rapid weight gain should be carefully investigated and if necessary appropriate supportive care and therapeutic measures should be undertaken. In clinical trials, there was an increased incidence of these events in elderly patients and those with a prior history of cardiac disease. Therefore, caution should be exercised in patients with cardiac dysfunction.* Listed in section 4.8 *Superficial oedemas were a common finding in all studies and were described primarily as periorbital or lower limb oedemas. However, these oedemas were rarely severe and may be managed with diuretics, other supportive measures, or by reducing the dose of imatinib.* *Miscellaneous adverse reactions such as pleural effusion, ascites, pulmonary oedema and rapid weight gain with or without superficial oedema may be collectively described as "fluid retention". These reactions can usually be managed by withholding imatinib temporarily and with diuretics and other appropriate supportive care measures. However, some of these reactions may be serious or life-threatening and several patients with blast crisis died with a complex clinical history of pleural effusion, congestive heart failure and renal failure. There were no special safety findings in paediatric clinical trials.* **Adverse reactions in clinical studies** General disorders and administration site conditions *Very common: Fluid retention and oedema* Eye disorders *Common: eyelid oedema* *Uncommon: orbital oedema, macular oedema* *Rare: papilloedema*	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Cardiac disorders *Uncommon: pulmonary oedema* Skin and subcutaneous tissue disorders *Very common: periorbital oedema* *Common: face oedema* *Rare: angioneurotic oedema* Reproductive system and breast disorders *Uncommon: scrotal oedema* **Adverse reactions from post-marketing reports** Nervous system disorders *Not known: cerebral oedema* Warning in section 4.9 *Adult population* *1200 to 1600 mg (duration varying between 1 to 10 days): oedema* Other routine risk minimisation measures *Therapy should be initiated by a physician experienced in the treatment of patients with haematological malignancies and malignant sarcomas, as appropriate.*	
CNS and gastrointestinal haemorrhages	Proposed text in SmPC ***Gastrointestinal haemorrhage*** Warning in section 4.4 *In the study in patients with unresectable and/or metastatic GIST, both gastrointestinal and intra-tumoural haemorrhages were reported (see section 4.8). Based on the available data, no predisposing factors (e.g. tumour size, tumour location, coagulation disorders) have been identified that place patients with GIST at a higher risk of either type of haemorrhage. Since increased vascularity and propensity for bleeding is a part of the nature and clinical course of GIST, standard practices and procedures for the monitoring and management of haemorrhage in all patients should be applied.* Listed in section 4.8 Gastrointestinal disorders *Uncommon: gastrointestinal haemorrhage (Abdominal pain and gastrointestinal haemorrhage were most commonly observed in GIST patients)* ***CNS haemorrhages*** Warning in section 4.8 **Adverse reactions in clinical studies** Nervous system disorders *Uncommon: cerebral haemorrhage* Other routine risk minimisation measures *Therapy should be initiated by a physician experienced in the treatment of patients with haematological malignancies and malignant sarcomas, as appropriate.*	None
Gastrointestinal obstruction, perforation or ulceration	Proposed text in SmPC Listed in section 4.8 **Adverse reactions in clinical studies** Gastrointestinal disorders *Uncommon: mouth ulceration, gastric ulcer* **Adverse reactions from post-marketing reports** Gastrointestinal disorders *Not known: Ileus/intestinal obstruction, gastrointestinal perforation* Other routine risk minimisation measures *Therapy should be initiated by a physician experienced in the treatment of patients with haematological malignancies and malignant sarcomas, as appropriate.*	None
Hepatotoxicity	Proposed text in SmPC Warning in section 4.2 *If elevations in bilirubin > 3 x institutional upper limit of normal (IULN) or in liver transaminases > 5 x IULN occur, imatinib should be withheld until bilirubin levels have returned to < 1.5 x IULN and transaminase levels to < 2.5 x IULN. Treatment with imatinib may then be continued at a reduced daily dose.* Warning in section 4.4 *Hepatotoxicity* *Metabolism of imatinib is mainly hepatic, and only 13% of excretion is through the kidneys. In patients with hepatic dysfunction (mild, moderate or severe), peripheral blood counts and liver enzymes should be carefully monitored (see sections 4.2, 4.8 and 5.2). It should be noted that GIST patients may have*	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	hepatic metastases which could lead to hepatic impairment. Cases of liver injury, including hepatic failure and hepatic necrosis, have been observed with imatinib. When imatinib is combined with high dose chemotherapy regimens, an increase in serious hepatic reactions has been detected. Hepatic function should be carefully monitored in circumstances where imatinib is combined with chemotherapy regimens also known to be associated with hepatic dysfunction (see sections 4.5 and 4.8). *Laboratory tests* *Liver function (transaminases, bilirubin, alkaline phosphatase) should be monitored regularly in patients receiving imatinib.* Listed in section 4.8 **Adverse reactions in clinical studies** Hepatobiliary disorders *Common: Increased hepatic enzymes* *Uncommon: Hyperbilirubinaemia, hepatitis, jaundice* *Rare: Hepatic failure, hepatic necrosis* *Some fatal cases of hepatic failure and of hepatic necrosis have been reported.* **Adverse reactions from post-marketing reports** *Severe elevation of transaminases (<5%) or bilirubin (<1%) was seen in CML patients and was usually managed with dose reduction or interruption (the median duration of these episodes was approximately one week). Treatment was discontinued permanently because of liver laboratory abnormalities in less than 1% of CML patients. In GIST patients (study B2222), 6.8% of grade 3 or 4 ALT (alanine aminotransferase) elevations and 4.8% of grade 3 or 4 AST (aspartate aminotransferase) elevations were observed. Bilirubin elevation was below 3%.* *There have been cases of cytolytic and cholestatic hepatitis and hepatic failure; in some of them outcome was fatal, including one patient on high dose paracetamol.* Section 5.2 *Although the results of pharmacokinetic analysis showed that there is considerable inter-subject variation, the mean exposure to imatinib did not increase in patients with varying degrees of liver dysfunction as compared to patients with normal liver function.* Other routine risk minimisation measures *Therapy should be initiated by a physician experienced in the treatment of patients with haematological malignancies and malignant sarcomas, as appropriate.*	
Skin rashes and severe cutaneous reactions	Proposed text in SmPC Listed in section 4.8 **Adverse reactions in clinical studies** *Very common: Dermatitis/eczema/rash* *Common: Erythema* *Uncommon: Rash pustular, dermatitis exfoliative, petechiae, psoriasis, purpura, bullous eruptions* *Rare: Acute febrile neutrophilic dermatosis (Sweet's syndrome), rash vesicular, erythema multiforme, leucocytoclastic vasculitis, Stevens-Johnson syndrome, acute generalised exanthematous pustulosis (AGEP)* **Adverse reactions from post-marketing reports** Skin and subcutaneous tissue disorders *Not know: Palmoplantar erythrodysesthesia syndrome, lichenoid keratosis, lichen planus, toxic epidermal necrolysis* Other routine risk minimisation measures *Therapy should be initiated by a physician experienced in the treatment of patients with haematological malignancies and malignant sarcomas, as appropriate.*	None
Hypothyroidism	Proposed text in SmPC Warning in section 4.4 *Hypothyroidism* *Clinical cases of hypothyroidism have been reported in thyroidectomy patients undergoing levothyroxine replacement during treatment with imatinib (see section 4.5). Thyroid stimulating hormone (TSH) levels should be closely monitored in such patients.* Other routine risk minimisation measures *Therapy should be initiated by a physician experienced in the treatment of patients with haematological malignancies and malignant sarcomas, as appropriate.*	None
Hypophosphatemia	Proposed text in SmPC Listed in section 4.8 **Adverse reactions in clinical studies** Metabolism and nutrition disorders *Uncommon: hypophosphatemia*	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Other routine risk minimisation measures *Therapy should be initiated by a physician experienced in the treatment of patients with haematological malignancies and malignant sarcomas, as appropriate.*	
Cardiac failure	Proposed text in SmPC Warning in section 4.4 *Patients with cardiac disease* *Patients with cardiac disease, risk factors for cardiac failure or history of renal failure should be monitored carefully, and any patient with signs or symptoms consistent with cardiac or renal failure should be evaluated and treated.* *In patients with hypereosinophilic syndrome (HES) with occult infiltration of HES cells within the myocardium, isolated cases of cardiogenic shock/left ventricular dysfunction have been associated with HES cell degranulation upon the initiation of imatinib therapy. The condition was reported to be reversible with the administration of systemic steroids, circulatory support measures and temporarily withholding imatinib. As cardiac adverse events have been reported uncommonly with imatinib, a careful assessment of the benefit/risk of imatinib therapy should be considered in the HES/CEL population before treatment initiation.* Listed in section 4.8 **Adverse reactions in clinical studies** Cardiac disorders *Uncommon: cardiac failure congestive (On a patient-year basis, cardiac events including congestive heart failure were more commonly observed in patients with transformed CML than in patients with chronic CML)* *Rare: myocardial infarction, angina pectoris* Other routine risk minimisation measures *Therapy should be initiated by a physician experienced in the treatment of patients with haematological malignancies and malignant sarcomas, as appropriate.*	None
Acute renal failure	Proposed text in SmPC Warning in section 4.2 *Renal insufficiency: Patients with renal dysfunction or on dialysis should be given the minimum recommended dose of 400 mg daily as starting dose. However, in these patients caution is recommended. The dose can be reduced if not tolerated. If tolerated, the dose can be increased for lack of efficacy (see sections 4.4 and 5.2).* Warning in section 4.4 *In patients with impaired renal function, imatinib plasma exposure seems to be higher than that in patients with normal renal function, probably due to an elevated plasma level of alpha-acid glycoprotein (AGP), an imatinib-binding protein, in these patients. Patients with renal impairment should be given the minimum starting dose. Patients with severe renal impairment should be treated with caution. The dose can be reduced if not tolerated (see sections 4.2 and 5.2).* Listed in section 4.8 **Adverse reactions in clinical studies** Renal and urinary disorders *Uncommon: renal failure acute* Warning in section 5.2 *Organ function impairment* *Imatinib and its metabolites are not excreted via the kidney to a significant extent. Patients with mild and moderate impairment of renal function appear to have a higher plasma exposure than patients with normal renal function. The increase is approximately 1.5 to 2 fold, corresponding to a 1.5 fold elevation of plasma AGP, to which imatinib binds strongly. The free drug clearance of imatinib is probably similar between patients with renal impairment and those with normal renal function, since renal excretion represents only a minor elimination pathway for imatinib (see sections 4.2 and 4.4).* Other routine risk minimisation measures *Therapy should be initiated by a physician experienced in the treatment of patients with haematological malignancies and malignant sarcomas, as appropriate.*	None
Severe respiratory adverse reactions	Proposed text in SmPC Listed in section 4.8 **Adverse reactions in clinical studies** Respiratory, thoracic and mediastinal disorders *Rare: pulmonary fibrosis, pulmonary hypertension, pulmonary haemorrhage* **Adverse reactions from post-marketing reports** Respiratory, thoracic and mediastinal disorders *Not known: Acute respiratory failure (fatal cases have been reported in patients with advanced disease, severe infections, severe neutropenia and other serious concomitant conditions), interstitial lung disease* Other routine risk minimisation measures *Therapy should be initiated by a physician experienced in the treatment of patients with haematological*	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	malignancies and malignant sarcomas, as appropriate.	
Rhabdomyolysis and myopathy	Proposed text in SmPC Listed in section 4.8 **Adverse reactions in clinical studies** Musculoskeletal and connective tissue disorders *Rare: rhabdomyolysis/myopathy* Other routine risk minimisation measures *Therapy should be initiated by a physician experienced in the treatment of patients with haematological malignancies and malignant sarcomas, as appropriate.*	None
Ovarian haemorrhage and haemorrhagic ovarian cyst	Proposed text in SmPC Listed in section 4.8 **Adverse reactions in clinical studies** *Rare: Haemorrhagic corpus luteum/ haemorrhagic ovarian cyst* Other routine risk minimisation measures *Therapy should be initiated by a physician experienced in the treatment of patients with haematological malignancies and malignant sarcomas, as appropriate.*	None
Tumour lysis syndrome	Proposed text in SmPC Warning in section 4.4 *Tumor lysis syndrome* *Due to the possible occurrence of tumour lysis syndrome (TLS), correction of clinically significant dehydration and treatment of high uric acid levels are recommended prior to initiation of imatinib (see section 4.8).* Listed in section 4.8 **Adverse reactions in clinical studies** Neoplasm benign, malignant and unspecified (including cysts and polyps) *Rare: Tumour lysis syndrome* **Adverse reactions from post-marketing reports** Neoplasm benign, malignant and unspecified (including cysts and polyps) *Not known: Tumour haemorrhage/tumour necrosis* Other routine risk minimisation measures *Therapy should be initiated by a physician experienced in the treatment of patients with haematological malignancies and malignant sarcomas, as appropriate.*	None
Growth retardation in children	Proposed text in SmPC Warning in section 4.4 *Paediatric population* *There have been case reports of growth retardation occurring in children and pre-adolescents receiving imatinib. The long-term effects of prolonged treatment with imatinib on growth in children are unknown. Therefore, close monitoring of growth in children under imatinib treatment is recommended (see section 4.8).* Listed in section 4.8 **Adverse reactions from post-marketing reports** Musculoskeletal and connective tissue disorders *Not known: Growth retardation in children* Other routine risk minimisation measures *Therapy should be initiated by a physician experienced in the treatment of patients with haematological malignancies and malignant sarcomas, as appropriate.*	None
Interaction with strong CYP3A4 inhibitors	Proposed text in SmPC Warning in section 4.5 *Active substances that may increase imatinib plasma concentrations:* *Substances that inhibit the cytochrome P450 isoenzyme CYP3A4 activity (e.g. protease inhibitors such as indinavir, lopinavir/ritonavir, ritonavir, saquinavir, telaprevir, nelfinavir, boceprevir; azole antifungals including ketoconazole, itraconazole, posaconazole, voriconazole; certain macrolides such as erythromycin, clarithromycin and telithromycin) could decrease metabolism and increase imatinib concentrations. There was a significant increase in exposure to imatinib (the mean Cmax and AUC of imatinib rose by 26% and 40%, respectively) in healthy subjects when it was co-administered with a single dose of ketoconazole (a CYP3A4 inhibitor). Caution should be taken when administering imatinib with inhibitors of the CYP3A4 family.* Other routine risk minimisation measures *Therapy should be initiated by a physician experienced in the treatment of patients with haematological malignancies and malignant sarcomas, as appropriate.*	None
Interaction with strong	Proposed text in SmPC Warning in section 4.4	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
CYP3A4 inducers	*Concomitant use of imatinib and medicinal products that induce CYP3A4 (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital or Hypericum perforatum, also known as St. John's Wort) may significantly reduce exposure to imatinib, potentially increasing the risk of therapeutic failure. Therefore, concomitant use of strong CYP3A4 inducers and imatinib should be avoided (see section 4.5).* Warning in section 4.5 *Active substances that may decrease imatinib plasma concentrations:* *Substances that are inducers of CYP3A4 activity e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital, fosphenytoin, primidone or Hypericum perforatum, also known as St. John's Wort) may significantly reduce exposure to imatinib, potentially increasing the risk of therapeutic failure. Pretreatment with multiple doses of rifampicin 600 mg followed by a single 400 mg dose of imatinib resulted in decrease in Cmax and AUC(0-∞) by at least 54% and 74%, of the respective values without rifampicin treatment. Similar results were observed in patients with malignant gliomas treated with imatinib while taking enzyme-inducing anti-epileptic drugs (EIAEDs) such as carbamazepine, oxcarbazepine and phenytoin. The plasma AUC for imatinib decreased by 73% compared to patients not on EIAEDs. Concomitant use of rifampicin or other strong CYP3A4 inducers and imatinib should be avoided.* Other routine risk minimisation measures *Therapy should be initiated by a physician experienced in the treatment of patients with haematological malignancies and malignant sarcomas, as appropriate.*	
Interaction with drugs eliminated by CYP3A4	Proposed text in SmPC Warning in section 4.4 *When imatinib is co-administered with other medicinal products, there is a potential for medicinal product interactions. Caution should be used when taking imatinib with CYP3A4 substrates with a narrow therapeutic window (e.g. cyclosporine, pimozide, tacrolimus, sirolimus, ergotamine, diergotamine, fentanyl, alfentanil, terfenadine, bortezomib, docetaxel, quinidine) or warfarin and other coumarin derivatives (see section 4.5).* Warning in section 4.5 *Active substances that may have their plasma concentration altered by imatinib* *Imatinib increases the mean Cmax and AUC of simvastatin (CYP3A4 substrate) 2- and 3.5 fold, respectively, indicating an inhibition of the CYP3A4 by imatinib. Therefore, caution is recommended when administering imatinib with CYP3A4 substrates with a narrow therapeutic window (e.g. cyclosporine, pimozide, tacrolimus, sirolimus, ergotamine, diergotamine, fentanyl, alfentanil, terfenadine, bortezomib, docetaxel and quinidine). Imatinib may increase plasma concentration of other CYP3A4 metabolised medicinal products (e.g. triazolo-benzodiazepines, dihydropyridine calcium channel blockers, certain HMG CoA reductase inhibitors, i.e. statins, etc.).* Other routine risk minimisation measures *Therapy should be initiated by a physician experienced in the treatment of patients with haematological malignancies and malignant sarcomas, as appropriate.*	None
Second malignancies in survivors	Proposed text in SmPC Warning in section 5.3 *In the 2 year rat carcinogenicity study administration of imatinib at 15, 30 and 60 mg/kg/day resulted in a statistically significant reduction in the longevity of males at 60 mg/kg/day and females at ≥ 30 mg/kg/day. Histopathological examination of decedents revealed cardiomyopathy (both sexes), chronic progressive nephropathy (females) and preputial gland papilloma as principal causes of death or reasons for sacrifice. Target organs for neoplastic changes were the kidneys, urinary bladder, urethra, preputial and clitoral gland, small intestine, parathyroid glands, adrenal glands and non-glandular stomach.* *Papilloma/carcinoma of the preputial/clitoral gland were noted from 30 mg/kg/day onwards, representing approximately 0.5 or 0.3 times the human daily exposure (based on AUC) at 400 mg/day or 800 mg/day, respectively, and 0.4 times the daily exposure in children (based on AUC) at 340 mg/m2/day. The no observed effect level (NOEL) was 15 mg/kg/day. The renal adenoma/carcinoma, the urinary bladder and urethra papilloma, the small intestine adenocarcinomas, the parathyroid glands adenomas, the benign and malignant medullary tumours of the adrenal glands and the non-glandular stomach papillomas/carcinomas were noted at 60 mg/kg/day, representing approximately 1.7 or 1 times the human daily exposure (based on AUC) at 400 mg/day or 800 mg/day, respectively, and 1.2 times the daily exposure in children (based on AUC) at 340 mg/m2/day. The no observed effect level (NOEL) was 30 mg/kg/day.* Other routine risk minimisation measures *Therapy should be initiated by a physician experienced in the treatment of patients with haematological malignancies and malignant sarcomas, as appropriate.*	None
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.	None
Hypoglycaemia	No risk minimisation activities are proposed. There is a lack of conclusive data indicating causal relationship at this time. Should PV activities uncover	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	additional data, the risk will be communicated through the labelling and additional risk minimisation activities may be proposed if necessary.	
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.	None
Tolerability during pregnancy and pregnancy outcomes	Proposed text in SmPC Warning in section 4.6 *Pregnancy* *There are limited data on the use of imatinib in pregnant women. Studies in animals have however shown reproductive toxicity (see section 5.3) and the potential risk for the foetus is unknown. Imatinib should not be used during pregnancy unless clearly necessary. If it is used during pregnancy, the patient must be informed of the potential risk to the foetus. Women of childbearing potential must be advised to use effective contraception during treatment.* Warning in section 5.3 *When female rats were dosed 14 days prior to mating and through to gestational day 6, there was no effect on mating or on number of pregnant females. At a dose of 60 mg/kg, female rats had significant post-implantation foetal loss and a reduced number of live foetuses. This was not seen at doses ≤ 20 mg/kg.* *In an oral pre- and postnatal development study in rats, red vaginal discharge was noted in the 45 mg/kg/day group on either day 14 or day 15 of gestation. At the same dose, the number of stillborn pups as well as those dying between postpartum days 0 and 4 was increased. In the F1 offspring, at the same dose level, mean body weights were reduced from birth until terminal sacrifice and the number of litters achieving criterion for preputial separation was slightly decreased. F1 fertility was not affected, while an increased number of resorptions and a decreased number of viable foetuses was noted at 45 mg/kg/day. The no observed effect level (NOEL) for both the maternal animals and the F1 generation was 15 mg/kg/day (one quarter of the maximum human dose of 800 mg).* *Imatinib was teratogenic in rats when administered during organogenesis at doses ≥ 100 mg/kg, approximately equal to the maximum clinical dose of 800 mg/day, based on body surface area. Teratogenic effects included exencephaly or encephalocele, absent/reduced frontal and absent parietal bones. These effects were not seen at doses ≤ 30 mg/kg.* Other routine risk minimisation measures *Therapy should be initiated by a physician experienced in the treatment of patients with haematological malignancies and malignant sarcomas, as appropriate.*	None
Interaction with drugs eliminated by CYP2C9, CYP2C19 AND CYP2D6	Proposed text in SmPC Warning in section 4.5 *Active substances that may have their plasma concentration altered by imatinib* *In vitro imatinib inhibits the cytochrome P450 isoenzyme CYP2D6 activity at concentrations similar to those that affect CYP3A4 activity. Imatinib at 400 mg twice daily had an inhibitory effect on CYP2D6-mediated metoprolol metabolism, with metoprolol Cmax and AUC being increased by approximately 23% (90%CI [1.16 1.30]). Dose adjustments do not seem to be necessary when imatinib is co-administrated with CYP2D6 substrates; however caution is advised for CYP2D6 substrates with a narrow therapeutic window such as metoprolol. In patients treated with metoprolol clinical monitoring should be considered.* Other routine risk minimisation measures *Therapy should be initiated by a physician experienced in the treatment of patients with haematological malignancies and malignant sarcomas, as appropriate.*	None
Interaction with acetaminophen/paracetamol	Proposed text in SmPC Warning in section 4.5 *In vitro, imatinib inhibits paracetamol O glucuronidation with Ki value of 58.5 micromol/l. This inhibition has not been observed in vivo after the administration of imatinib 400 mg and paracetamol 1000 mg. Higher doses of imatinib and paracetamol have not been studied.* *Caution should therefore be exercised when using high doses of imatinib and paracetamol concomitantly.* Other routine risk minimisation measures *Therapy should be initiated by a physician experienced in the treatment of patients with haematological malignancies and malignant sarcomas, as appropriate.*	None
Paediatric patients: long term follow up	Proposed text in SmPC **Growth retardation** Warning in section 4.4 *Paediatric population* *There have been case reports of growth retardation occurring in children and pre-adolescents receiving imatinib. The long-term effects of prolonged treatment with imatinib on growth in children are unknown. Therefore, close monitoring of growth in children under imatinib treatment is recommended (see section 4.8).*	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Listed in section 4.8 **Adverse reactions from post-marketing reports** Musculoskeletal and connective tissue disorders *Not known: Growth retardation in children* **Second malignancy in survivors** Warning in section 5.3 *In the 2 year rat carcinogenicity study administration of imatinib at 15, 30 and 60 mg/kg/day resulted in a statistically significant reduction in the longevity of males at 60 mg/kg/day and females at ≥ 30 mg/kg/day. Histopathological examination of decedents revealed cardiomyopathy (both sexes), chronic progressive nephropathy (females) and preputial gland papilloma as principal causes of death or reasons for sacrifice. Target organs for neoplastic changes were the kidneys, urinary bladder, urethra, preputial and clitoral gland, small intestine, parathyroid glands, adrenal glands and non-glandular stomach.* *Papilloma/carcinoma of the preputial/clitoral gland were noted from 30 mg/kg/day onwards, representing approximately 0.5 or 0.3 times the human daily exposure (based on AUC) at 400 mg/day or 800 mg/day, respectively, and 0.4 times the daily exposure in children (based on AUC) at 340 mg/m2/day. The no observed effect level (NOEL) was 15 mg/kg/day. The renal adenoma/carcinoma, the urinary bladder and urethra papilloma, the small intestine adenocarcinomas, the parathyroid glands adenomas, the benign and malignant medullary tumours of the adrenal glands and the non-glandular stomach papillomas/carcinomas were noted at 60 mg/kg/day, representing approximately 1.7 or 1 times the human daily exposure (based on AUC) at 400 mg/day or 800 mg/day, respectively, and 1.2 times the daily exposure in children (based on AUC) at 340 mg/m2/day. The no observed effect level (NOEL) was 30 mg/kg/day.* Other routine risk minimisation measures *Therapy should be initiated by a physician experienced in the treatment of patients with haematological malignancies and malignant sarcomas, as appropriate.*	
Paediatric patients below 2 years of age	Proposed text in SmPC Warning in section 4.2 *Posology for CML in paediatric patients* *There is no experience with the treatment of children below 2 years of age.* *Special populations* *Paediatric use: There is no experience in children with CML below 2 years of age.* Other routine risk minimisation measures *Therapy should be initiated by a physician experienced in the treatment of patients with haematological malignancies and malignant sarcomas, as appropriate.*	None
Renal impairment	Proposed text in SmPC Warning in section 4.2 *Renal insufficiency: Patients with renal dysfunction or on dialysis should be given the minimum recommended dose of 400 mg daily as starting dose. However, in these patients caution is recommended. The dose can be reduced if not tolerated. If tolerated, the dose can be increased for lack of efficacy (see sections 4.4 and 5.2).* Warning in section 4.4 *In patients with impaired renal function, imatinib plasma exposure seems to be higher than that in patients with normal renal function, probably due to an elevated plasma level of alpha-acid glycoprotein (AGP), an imatinib-binding protein, in these patients. Patients with renal impairment should be given the minimum starting dose. Patients with severe renal impairment should be treated with caution. The dose can be reduced if not tolerated (see sections 4.2 and 5.2).* Section 4.8 **Adverse reactions in clinical studies** Renal and urinary disorders *Uncommon: renal failure acute, renal pain* Warning in section 5.2 *Organ function impairment* *Imatinib and its metabolites are not excreted via the kidney to a significant extent. Patients with mild and moderate impairment of renal function appear to have a higher plasma exposure than patients with normal renal function. The increase is approximately 1.5 to 2 fold, corresponding to a 1.5 fold elevation of plasma AGP, to which imatinib binds strongly. The free drug clearance of imatinib is probably similar between patients with renal impairment and those with normal renal function, since renal excretion represents only a minor elimination pathway for imatinib (see sections 4.2 and 4.4).* Other routine risk minimisation measures *Therapy should be initiated by a physician experienced in the treatment of patients with haematological malignancies and malignant sarcomas, as appropriate.*	None
Hepatic impairment	Proposed text in SmPC Warning in section 4.2 *Hepatic insufficiency: Imatinib is mainly metabolised through the liver. Patients with mild, moderate or severe liver dysfunction should be given the minimum recommended dose of 400 mg daily. The dose can be reduced if not tolerated (see sections 4.4, 4.8 and 5.2).*	None

<table>
<tr><th>Safety concern</th><th>Routine risk minimisation measures</th><th>Additional risk minimisation measures</th></tr>
<tr><td></td><td>Liver dysfunction classification:

<table><tr><th>Liver dysfunction</th><th>Liver function tests</th></tr><tr><td>Mild</td><td>Total bilirubin: = 1.5 ULN
AST: >ULN (can be normal or <ULN if total bilir</td></tr><tr><td>Moderate</td><td>Total bilirubin: >1.5-3.0 ULN
AST: any</td></tr><tr><td>Severe</td><td>Total bilirubin: >3-10 ULN
AST: any</td></tr></table>ULN = upper limit of normal for the institution
AST = aspartate aminotransferase

Warning in section 4.4
Liver function (transaminases, bilirubin, alkaline phosphatase) should be monitored regularly in patients receiving imatinib.

Listed in section 4.8
Adverse reactions in clinical studies
Hepatobiliary disorders
Common: Increased hepatic enzymes
Uncommon: Hyperbilirubinaemia, hepatitis, jaundice
Rare: Hepatic failure (Some fatal cases of hepatic failure and of hepatic necrosis have been reported), hepatic necrosis
Biochemistry
Severe elevation of transaminases (<5%) or bilirubin (<1%) was seen in CML patients and was usually managed with dose reduction or interruption (the median duration of these episodes was approximately one week). Treatment was discontinued permanently because of liver laboratory abnormalities in less than 1% of CML patients. In GIST patients (study B2222), 6.8% of grade 3 or 4 ALT (alanine aminotransferase) elevations and 4.8% of grade 3 or 4 AST (aspartate aminotransferase) elevations were observed. Bilirubin elevation was below 3%.

Warning in section 5.2
Although the results of pharmacokinetic analysis showed that there is considerable inter-subject variation, the mean exposure to imatinib did not increase in patients with varying degrees of liver dysfunction as compared to patients with normal liver function (see sections 4.2, 4.4 and 4.8).

Other routine risk minimisation measures
Therapy should be initiated by a physician experienced in the treatment of patients with haematological malignancies and malignant sarcomas, as appropriate.</td><td></td></tr>
<tr><td>Elderly patients</td><td>Proposed text in SmPC

Warning in section 4.2
Elderly patients: Imatinib pharmacokinetics has not been specifically studied in the elderly. No significant age-related pharmacokinetic differences have been observed in adult patients in clinical trials which included over 20% of patients age 65 and older. No specific dose recommendation is necessary in the elderly.

Other routine risk minimisation measures
Therapy should be initiated by a physician experienced in the treatment of patients with haematological malignancies and malignant sarcomas, as appropriate.</td><td>None</td></tr>
</table>

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

The CHMP endorsed this advice without changes.

2.7. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Glivec 400 mg film-coated tablets. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-Risk Balance

The application contains adequate quality, non-clinical and clinical data and the bioequivalence has been shown between Imatinib Actavis 400 mg hard capsules and Glivec 400 mg film-coated tablets under fed

conditions. A positive benefit/risk ratio comparable to the reference product can therefore be concluded. The RMP is acceptable.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Imatinib Actavis is not similar to Tasigna, Sprycel, Vidaza, Evoltra, Atriance, Xaluprine, Bosulif, Iclusig or Revlimid within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 8.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit 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.
- adult patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) integrated with chemotherapy.
- adult patients with relapsed or refractory Ph+ ALL as monotherapy.
- adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements.
- adult patients with advanced hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL) with FIP1L1-PDGFRα rearrangement.

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

Imatinib Actavis is indicated for:

- 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 DFSP. 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.

is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal products on restricted medical prescription, reserved for use in certain specialised areas (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

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

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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

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

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

Not applicable.