NOVARTIS

Chief Medical Office & Patient Safety

Imatinib

STI571

EU Safety Risk Management Plan

Active substance(s) (INN or common name):	Imatinib mesylate
Product(s) concerned (brand name(s)):	Glivec® / [Nationally completed name]
Document status:	Final
Version number:	13.0
Data lock point for this RMP	10-May-2021
Date of final sign off	09-Feb-2023

[redacted]

Template version 6.3, Effective from 24-Feb-2021

Rationale for submitting an updated RMP version 13.0

The current European Union (EU) Risk Management Plan (RMP) v 13.0 is prepared to be used for the following Marketing Authorization holders (MAHs):

- Novartis Europharm Limited
- Sandoz International GmBH

The clinical studies data presented in this RMP have been obtained by the MAH Novartis Europharm Limited for Glivec.

The current EU RMP v 13.0 has been updated to reflect the changes as below:

- Milestone update of RMP commitment for Category 1 study CSTI571I2201 titled 'A European observational registry collecting efficacy and safety data in newly diagnosed pediatric Philadelphia-positive (Ph+) Acute Lymphoblastic Leukemia (ALL) patients treated with chemotherapy + imatinib, with or without hematopoietic stem cell treatment (± HSCT)'. Study is completed.
- Removal of Missing information: 'Pediatric patients: Long term follow up'.
- Update that the product is no longer subject to additional monitoring in the EU.
- Removal of 'second primary malignancy (SPM) report' as other forms of routine pharmacovigilance activities as endorsed by EMA within the regulatory procedure, EMEA/H/C/000406/II/0115 dated, 16-Jan-2020.

Summary of significant changes in this RMP:

The table below presents the major changes made in the current RMP v 13.0 as compared to the previous RMP v 12.1.

Part	Major changes compared to RMP v12.1
Part I	Information aligned with the proposed SmPC
Part II – Module SI	No change
Part II – Module SII	No change
Part II – Module SIII	Update of clinical trial exposure data
Part II – Module SIV	No change
Part II – Module SV	Update the post authorization exposure data in alignment with last Glivec PSUR (reporting period: 11-May-2018 to 10-May-2021)
Part II – Module SVI	No change
Part II – Module SVII.1.	No change
Part II – Module SVII.2	Rationale for removal of Missing information of 'Pediatric patients: Long term follow up' was added
Part II – Module SVII.3	Update of risk tables
Part II – Module SVIII	Missing information of 'Pediatric patients: Long term follow up' was removed from the summary of safety concerns
Part III.1	Removal of 'second primary malignancy report' as other forms of routine pharmacovigilance activities
Part III.2	Update to reflect the completion of the additional pharmacovigilance study CSTI571I2201
Part III.3	Update to reflect the completion of the additional pharmacovigilance study CSTI571I2201

Part	Major changes compared to RMP v12.1
Part IV	No change
Part V.1	Deletion of the routine risk minimization measures for 'Pediatric patients: Long term follow up'
Part V.2	No change
Part V.3	Deletion of 'Pediatric patients: Long term follow up' details from the summary of risk minimization measures Reporting for second primary malignancy was removed from routine PhV activities beyond adverse drug reporting and signal detection
Part VI	Missing information of 'Pediatric patients: Long term follow up' was removed Post-authorization development plan was updated to reflect completion of CSTI571I2201 study Consistent changes made to align with other parts of the RMP
Part VII –Annexes	
Annex 1	No change
Annex 2	Updated to reflect completion of the additional pharmacovigilance study, CSTI571I2201
Annex 3	Part C (Previously agreed protocols for ongoing studies and final protocols not reviewed by the competent authority) status changed to 'none'
Annex 4	Specific adverse drug reaction follow-up form updated from v1.0 to v1.1 with minor administrative changes
Annex 5	No change
Annex 6	No change
Annex 7	Updated the 'brief statistical description and supportive outputs' Deletion of MedDRA search terms for spontaneous post-marketing data Update of the Internal References list
Annex 8	Updated to reflect the changes made to the current RMP v 13.0

Other RMP versions under evaluation

No RMP versions are currently under evaluation.

Details of the currently approved RMP:

MAH: Novartis Europharm Limited

- Version number: 12.1
- Approved with procedure: EMEA/H/C/000406/II/0115
- Date of approval (opinion date): 16-Jan-2020

MAH: Sandoz International GmBH

- Version number: 1.1
- Approved with procedure: NL/H/3318-3319/DC
- Date of approval (opinion date): 14-Oct-2015

QPPV name: Dr. David Lewis

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorization holder's QPPV. The electronic signature is available on file.

Table of contents

List of tables

List of abbreviations

ADR	Adverse Drug Reaction
ALL	Acute Lymphoblastic Leukemia
allo-SCT/allo-HSCT	allogeneic hematopoietic stem-cell transplantation
AP	Accelerated Phase
AUC	Area under the blood concentration-time curve
BCR-ABL	Chimeric BCR-ABL oncogene/ oncoprotein product of BCR-ABL fusion gene
BP	Blast phase
CEL	Chronic eosinophilic leukemia
CI	Confidence interval
CML	Chronic Myeloid Leukemia
CML-CP	Chronic Myeloid Leukemia in Chronic Phase
Cmax	Concentration Maximum
Cmin	Concentration Minimum
CNS	Central Nervous System
CSR	Clinical Study Report
CYP3A4	Cytochrome P450 3A4
DFSP	Dermatofibrosarcoma protuberans
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FPFV	First Patient First Visit
GI	Gastrointestinal
GIST	Gastrointestinal Stromal Tumor
HES	Hypereosinophilic syndrome
HIV	Human Immunodeficiency Viruses
HLA	human leukocyte antigen
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IFN	Interferon-α
iv	Intravenous
KIT/Kit	Stem cell factor receptor
LPLV	Last Patient Last Visit
MAH	Marketing authorization holder
MACDP	Metropolitan Atlanta Congenital Defects Program
MDS/MPD	Myelodysplastic/myeloproliferative diseases
MedDRA	Medical Dictionary for Regulatory Activities
PDGFR	Platelet-derived growth factor receptor
Ph+	Philadelphia chromosome positive
Ph+ CML	Philadelphia chromosome positive chronic myeloid leukemia
Ph+ ALL	Philadelphia chromosome positive acute lymphoblastic leukemia
PIP	Pediatric Investigational Plan

PK	Pharmacokinetic
PL	Patient Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PTY	Patient treatment Years
QPPV	Qualified Person for Pharmacovigilance
RMP	Risk Management Plan
SAE	Serious Adverse Event
SCAR	Serious Cutaneous Adverse Reaction
SD	Standard deviation
SDS	Standard-deviation score
SIR	Standardized Incidence Rate
SmPC	Summary of Product Characteristics
TK	Tyrosine kinase
TKI	Tyrosine kinase inhibitor
UK	United Kingdom
USA	United States of America
WBC	White blood cell

1 Part I: Product(s) Overview

Table 1-1 Part I.1 - Product Overview

Active substance (INN or common name)	Imatinib mesylate
Pharmacotherapeutic group(s) (ATC Code)	Protein-tyrosine kinase inhibitor (TKI) (L01EA01)
Marketing Authorization Holder	Novartis Europharm Limited Sandoz International GmBH
Medicinal products to which this RMP refers	2
Invented name(s) in the European Economic Area (EEA)	GLIVEC® / [Nationally completed name]
Marketing authorization procedure	Centralized for Novartis Europharm Limited Decentralized for Sandoz International GmBH
Brief description of the product	**Chemical class:** protein-tyrosine kinase inhibitor
	Summary of mode of action: Imatinib is a small molecule protein-TKI that potently inhibits the activity of the BCR-ABL tyrosine kinase (TK), as well as several receptor TKs: Kit, the receptor for stem cell factor (SCF) coded for by the c-Kit proto-oncogene, the discoidin domain receptors (DDR1) and DDR2), the colony stimulating factor receptor (CSF-1R) and the platelet-derived growth factor receptors alpha and beta (PDGFR-alpha and PDGFR-beta). Imatinib can also inhibit cellular events mediated by activation of these receptor kinases.
	Important information about its composition: Glivec is available as 100 mg imatinib mesylate in the hard gelatin capsules and as 100 mg and 400 mg imatinib mesylate in the film-coated tablets. The inactive ingredients include colloidal silicon dioxide (silica, colloidal anhydrous), crospovidone, magnesium stearate, and microcrystalline cellulose (cellulose, microcrystalline). The capsule shells contain yellow iron oxide, gelatin, and titanium dioxide. **For Sandoz:** Imatinib is available as 100 mg and 400 mg imatinib mesylate in the film-coated tablets. The inactive ingredients include colloidal silicon dioxide (silica, colloidal anhydrous), crospovidone, magnesium stearate, and microcrystalline cellulose (cellulose, microcrystalline). The capsule shells contain yellow iron oxide, gelatin and titanium dioxide.
Hyperlink to the Product Information	[Proposed SmPC] Current approved SmPC
Indication(s) in the EEA	**Current: MAH Novartis and Sandoz** - treatment of adult and pediatric patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) for whom bone marrow transplantation is not considered as the first line of treatment

	- treatment of adult and pediatric patients with Ph+ CML in chronic phase (CML-CP) after failure of interferon-alpha therapy, or in accelerated phase or blast crisis. - treatment of adult and pediatric patients with newly diagnosed Ph+ acute lymphoblastic leukemia (Ph+ ALL) integrated with chemotherapy - treatment of adult patients with relapsed or refractory Ph+ ALL as monotherapy - treatment of adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements - treatment of adult patients with advanced hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) with F1P1L1-PDGFRα rearrangement. - 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. **Current: MAH Novartis only** - treatment of adult patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (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
	Proposed: Not applicable
Dosage in the EEA	**Current – MAH Novartis and Sandoz** **CML (adult patients)**: The recommended dose of Glivec/ Imatinib is 400 mg/day once daily for patients in chronic phase CML and 600 mg/day once daily for patients in accelerated phase and blast crisis. **CML (children)**: Dosing for children should be on the basis of body surface area (mg/m^2). The dose of 340 mg/m^2 daily is recommended for children with chronic phase CML and advanced phase CML (not to exceed the total dose of 600 mg/day). **Ph+ ALL (adult patients)**: The recommended dose of Glivec/ Imatinib is 600 mg/day. **Ph+ ALL (children)**: Dosing for children should be on the basis of body surface area (mg/m^2). The dose of 340 mg/m^2 daily is recommended for children with Ph+ ALL (not to exceed the total dose of 600 mg/day). **MDS/MPD (adult patients)**: The recommended dose of Glivec/ Imatinib is 400 mg/day. **HES/CEL (adult patients)**: The recommended dose of Glivec/ Imatinib is 100 mg/day. **GIST (adult patients)**: The recommended dose of Glivec/ Imatinib is 400 mg/day for patients with unresectable and/or metastatic malignant GIST. **DFSP (adult patients)**: The recommended dose of Glivec/ Imatinib is 800 mg/day. The detailed description of posology is available in the Summary of Product Characteristics (SmPC).

	Route of administration: Oral
	Proposed: None
Pharmaceutical form(s) and strengths	**Current**: Film coated tablets 100 mg and 400 mg (Novartis and Sandoz); Hard capsules 100 mg (Novartis only)
	Proposed: None
Is/will the product be subject to additional monitoring in the EU?	No (MAH Novartis) No (MAH Sandoz)

2 Part II Safety specification Module SI: Epidemiology of the indication(s) and target population

2.1 Indication: Chronic Myeloid Leukemia

Incidence

CML is the most common of the myeloproliferative neoplasm and it accounts for approximately 12% of all cases of leukemia (Siegel et al 2015). In Europe, based on data from the HAEMACARE project, the incidence of CML for the period 2000-2002 was 1.10 cases per 100000 population [95% confidence intervals (CI): 1.06-1.15], with the highest age-standardized rates per 100000 observed in southern countries (incidence rate 1.16) and the lowest in northern countries, and United Kingdom (UK) and Ireland (incidence rate 0.85) (Sant et al 2010). According to the EUTOS population-based registry that registered patients across 20 countries in Europe between 2008 and 2012, the age-standardized incidence of CML was 0.96 per 100000 per year (Hoffmann et al 2015). In the United States, it was estimated that there would be 8990 new patients with CML in 2019 (SEER 2019).

Table 2-1 Estimated number of incident cases in EU in the year 2016

Countries	Incident cases of CML		
	Male	Female	Both male and Female
France	584	360	944
Germany	767	662	1428
Italy	628	400	1029
Spain	398	230	628
United Kingdom	453	350	803
EU-28	3933	2645	6578
Source: GBD 2019			

Prevalence

There has been a growth in the prevalence of CML since the introduction of imatinib in 2001. In 2011, the number of people in the US, living with CML, had doubled since 2001 and this trend is expected to continue (Shah and Arceci 2012). In 2016, there were an estimated 54,226 people living with CML in the US (SEER 2019). According to RARECARENet (2008), the prevalence of CML in Europe was 32, 412 persons in 2008. Data on prevalence of CML in the EU are limited. In a study in Sweden, the complete prevalence estimate for 2012 was 1.2 per 10,000 population (Gunnarsson et al 2016). In a German study, the estimated complete prevalence for 2012 was 1.1 per 10,000 population (1.2 and 1.1 per 10,000 population in males and females, respectively) in Germany (Lauseker et al 2016). In a study in the UK, the complete prevalence was 1.5 per 10,000 population (1.7 and 1.3 in males and females, respectively) (Li et al 2016).

Demographics of the population in the authorized indication – age, sex, racial and/or ethnic origin and risk factors for the disease

The median age of diagnosis of CML was 65 years, according to SEER data from 2012 to 2016 (SEER 2019). Approximately 2.0% were diagnosed under the age of 20 years, 7.9% between 20 and 34 years, 8.1% between 35 and 44 years, 13.5% between 45 and 54 years, 18.0% between 55 and 64 years, 21.5% between 65 and 74 years, 19.4% between 75 and 84 years, and 9.6% over 84 years of age.

Table 2-2 Incident rates by race and sex adjusted to the US population

Race/Ethnicity	Men (/100000 men)	Women (/100000 women)
All Races	2.4	1.4
White	2.5	1.5
Black	2.2	1.5
Asian/Pacific Islander	1.7	0.8
American Indian/Alaska Native	2.0	1.0
Hispanic	1.9	1.2
Source: SEER 2019.		

In a case-control study in Minnesota (US) that compared 670 patients with myeloid leukemia (420 patients with acute myeloid leukemia and 186 patients with CML) and 701 population-based controls, a statistically significant association was observed between peptic ulcer and CML (OR 2.0; 95% CI: 1.1-3.8). A personal history of cancer also increased the risk for CML (OR 3.5; 95% CI: 2.0-5.8). This association remained significant after adjusting for previous radiation or chemotherapy treatment (OR 3.6; 95% CI: 1.9-7.0) (Johnson et al 2012). Exposure to ionizing radiation has been reported as a risk factor. There is no known familial disposition to CML and it is unknown whether specific genetic variants predispose persons in the general population to develop CML. Some studies of families in which multiple members have developed myeloproliferative neoplasms including CML have suggested the presence of an autosomal dominant mutation that may predispose to acquisition of a secondary somatic mutation such as the Ph chromosome translocation or JAK2 mutation. A genome-wide association study of Korean and European cohorts suggested that persons with genetic variants at two chromosomal loci, 6q25.1 and 17p11.1, may be more likely to develop CML (Kim et al 2011).

The main existing treatment options

When a patient has suspected CML prior to confirmation of the diagnosis, therapy with hydroxyurea may be used to reduce white blood cells (WBC) counts close to normal levels. Treatment is continued until the confirmation of Ph+ chromosome. When the diagnosis of CML is confirmed, the therapy with Tyrosine kinase inhibitors (TKIs) starts (Cortes and Kantarjian 2012).

From 2000 to 2005 patients were treated with imatinib at different doses (400mg daily or 800 mg daily). One study compared the two doses of imatinib (TOPS trial) and showed no difference in the major molecular response rate at 1 year, despite somewhat faster achievement of rates of major molecular response (MMR) with the higher dose.

Since 2005, second generation TKIs (dasatinib, nilotinib, bosutinib, ponatinib) provided higher rates of early responses in CML treated patients compared with imatinib, with nearly 90% of patients achieving complete cytogenetic response by 3 months of therapy and also excellent event free survival and transformation-free survival (Cortes and Kantarjian 2012).

The combination of interferon alpha with imatinib has been suggested as a possible treatment to improve the rate of major molecular response or superior molecular response (Simonsson et al 2011, Preudhomme et al 2010).

Patients most commonly start therapy with imatinib or with second generation TKIs as initial treatment although the safety profiles of the compounds differ and patient history should be considered.

The European Leukemia Network recommendations suggested the following treatment approach (Baccarani et al 2013, Baccarani et al 2015).

Table 2-3 Treatment approach by EU Leukemia Network recommendations

CML Chronic phase First line	
All patients	Imatinib 400 mg daily, nilotinib 300 mg bid, or dasatinib 100 mg daily Human leukocyte antigen (HLA) type patients and siblings only in case of baseline warnings (high risk, major route clonal chromosomal abnormalities in Ph+ cells (CCA/Ph1))
Second line, intolerance to the first TKI	
Anyone of the other TKIs approved first line (imatinib, nilotinib, dasatinib)	
Second line, failure of imatinib first line	Dasatinib or nilotinib or bosutinib or ponatinib HLA type patients and siblings
Second line, failure of nilotinib first line	Dasatinib or bosutinib or ponatinib HLA type patients and siblings; search for an unrelated stem cell donor; consider allogeneic hematopoietic stem-cell transplantation (allo-SCT)
Second line, failure of dasatinib first line	Nilotinib or bosutinib or ponatinib HLA type patients and siblings; search for an unrelated stem cell donor; consider allo-SCT
Third line, failure of and/or intolerance to 2 TKIs	
	Anyone of the remaining TKIs; allo-SCT recommended in all eligible patients
Any line, T315I mutation	Ponatinib HLA type patients and siblings; search for an unrelated stem cell donor; consider allo-SCT
CML Accelerated phase (AP) and blast phase (BP)	
AP and BP in newly diagnosed, TKI-naive patients	Imatinib 400 mg twice daily or dasatinib 70 mg twice daily or 140 mg once daily. Stem cell donor search. Then, allo-SCT is recommended for all BP patients and for the AP patients who do not achieve an optimal response.

	Chemotherapy may be required before allo-SCT, to control the disease.
AP and BP as a progression from CP in TKI-pretreated patients	Any of the TKIs that were not used before progression (ponatinib in case of T315I mutation), then allo-SCT in all patients. Chemotherapy is frequently required to make patients eligible for allo-SCT.
Abbreviations: allo-SCT, allogeneic hematopoietic stem-cell transplantation; AP, accelerated phase; BP, blast phase; CP, chronic Phase; CML, chronic myeloid leukemia	

Also approved, for patients in whom prior TKI therapy fails, are radotinib, which is available in Korea, and omacetaxine, which is a non-TKI drug approved by the US Food and Drug Administration (FDA) (Baccarani et al 2013).

Natural history of the indicated condition in the population, including mortality and morbidity:

In the US from 2012-2016, the median age at death for CML was 77 years.

Approximately 0.5% died under age 20

- 2.8% between the ages of 20 and 34 years
- 3.6% between the ages of 35 and 44 years
- 6.9% between the ages of 45 and 54 years
- 11.6% between the ages of 55 and 64 years
- 18.2% between the ages of 65 and 74 years
- 30.0% between the ages of 75 and 84 years
- 26.4% 84+ years of age.

The age-adjusted death rate was 0.3 per 100000 men and women per year (SEER 2019).

Table 2-4 Mortality and morbidity

Race/Ethnicity	Men (/100000 men)	Women (/100000 women)
All Races	0.4	0.2
White	0.4	0.2
Black	0.4	0.2
Asian/Pacific Islander	0.2	0.1
American Indian/Alaska Native	N/A	N/A
Hispanic	0.3	0.2
N/A: Statistic not displayed due to less than 16 cases; SEER 2019		

Millot et al (2005) published the signs and symptoms at the time of diagnosis of 40 children and adolescents treated for CML in 16 French centers. The clinical features at diagnosis (in 430 patients) over a 16-year period is presented in Table 2-5.

Table 2-5 Symptoms at diagnosis of CML patients

Symptom (children-adolescent / all ages)	Children and adolescent (%)	All ages (%)
Asthenia / fatigue or lethargy	45	33.5
Abdominal fullness	7.5	14.8
Abdominal pain	5	-
Ankle oedema	-	2.2
Anorexia	2.5	-
Arthralgia	-	4.0
Bleeding	17.5	21.3
Bone pain	7.5	7.4
Chest pain/dyspnea	5	4.5
Cough	2.5	3.1
Dizziness	-	2.2
Fever/sweats	10	14.6
Headache	2.5	5.8
Hearing disturbance	2.5	0.2
Infection	-	6.2
Malaise	-	3.1
Mental change (somnolence, inability to concentrate, memory loss, depression)	-	1.6
Nausea/vomiting	2.5	2.2
Priapism	4	1.9
Splenic discomfort	20	18.6
Visual disturbances	2.5	4.4
Weakness	-	4.4
Weight loss	17.5	20.0

Source: Millot et al (2005), Savage et al (1997).

Important co-morbidities

A retrospective cohort study on 878 CML patients was performed in two US administrative claims databases from 1997 to 2011. The study intended to analyze clinical and economic outcomes and treatment adherence of nilotinib and dasatinib as second-line treatments in imatinib resistant or intolerant patients. Diseases were identified using reported International classification of diseases-9th revision-clinical modification (ICD-9-CM) codes in medical claims. This type of study has limitations since there may be some inaccuracies in coding diagnosis and procedures and they do not include patient's complete profile or relevant disease risk factors such as family history or disease severity. Table 2-6 summarizes the comorbidities of those patients before they started treatment with nilotinib or dasatinib (Guerin et al 2012).

Table 2-6 Comorbidities (%) in adult CML patients starting second-line therapy

Comorbidity	Nilotinib patients (n=328)	Dasatinib patients (n=550)	P Value
Anemia	72.0	65.5	0.046*

Comorbidity	Nilotinib patients (n=328)	Dasatinib patients (n=550)	P Value
Chronic pulmonary disease	21.0	17.1	ns
Cardiovascular disease	22.6	17.8	ns
Cerebrovascular disease	8.5	9.5	ns
Congestive heart failure	5.2	4.9	ns
Coagulopathy	12.8	14.4	ns
Depression	17.4	10.9	0.006*
Diabetes	23.2	22.2	ns
Fibromyalgia	7.3	11.6	0.039*
Fluid electrolyte disorders	19.5	15.6	ns
Hyperlipidemia	43.0	34.0	0.008*
Hypertension	47.3	38.5	0.011*
Hypothyroidism	12.8	11.5	ns
Liver disease	5.5	5.8	ns
Lymphoma	11.0	10.2	ns
Macular degeneration	5.2	4.7	ns
Neurologic disorders	7.0	4.9	ns
Obesity	6.1	7.8	ns
Osteoporosis	8.5	5.3	ns
Peripheral vascular disease	13.4	6.4	<0.001*
Psychoses	9.5	6.4	ns
Renal failure	17.7	4.9	ns
Solid tumor	17.7	15.3	ns
Valvular disease	19.5	12.4	0.004*

*significant at the 5% level
ns: non-significant

Gugliotta et al (2013) reviewed studies reporting the effect of comorbidities in the treatment of CML with TKIs. Most of the retrieved studies used different co-morbidities indexes that did not allow to having separate information about those specific co-morbidities. However, a sub-analysis of the DASISION study to assess the impact of baseline comorbidities on the safety and efficacy of first-line dasatinib and imatinib in Chronic Myeloid Leukemia in Chronic Phase (CML-CP) patients reported that 48% of patients on dasatinib and 46% on imatinib had two or more comorbidities. In order of frequency; gastrointestinal (33-35%), muscle-skeletal (27-31%), endocrine-metabolic (excluding diabetes 17-21%), cardiovascular (CV) (13-17%), respiratory (13-14%), dermatologic (12%), hepatobiliary (9-12%), hyperlipidemia (7-9%), diabetes mellitus (5-7%), and renal (5-7%).

2.2 Indication: Ph+ Acute Lymphoblastic Leukemia (ALL)

Incidence

ALL has a bimodal incidence distribution. The first peak of incidence of 4-5 per 100000 population occurs between the ages of 2-4 years. Then the incidence decreases with age before

a second, smaller peak of 1 per 100000 population occurs in patients older than 50 years (Faderl et al (2003), Terracini (2011)). ALL represents 78% of all leukemias in children below the age of 15 years (Siegel et al 2012) and 12% in adults (Jemal et al 2003). In patients with ALL, the incidence of Ph+ ALL increases with age from 5% or less in children, 20% in young adults, and up to 40-50% in older patients (>50 years) (Maino et al 2014).

Table 2-7 Estimated number of incident cases of ALL in the EU in the year 2016

Countries	Incident cases of ALL		
	Male	Female	Both male and Female
France	236	140	376
Germany	339	206	545
Italy	311	207	518
Spain	170	104	274
United Kingdom	212	150	363
EU-28	2097	1295	3392

Source: GBD 2019a

Prevalence

In 2016, the prevalence of ALL (regardless of cytogenic and molecular abnormalities) in the US was approximately 95,764 people (SEER 2019a). According to Orphanet, a consortium of 40 countries within Europe and across the globe, the prevalence of ALL is about 1-5 per 10,000 people (Orphanet 2007). Prevalence by age and race is presented in Table 2-8.

Demographics of the population in the authorized indication – age, sex, racial and/or ethnic origin and risk factors for the disease

ALL is more prevalent in males than females and in Hispanics and whites than blacks and Asian/Pacific Islanders. The table below (Table 2-8) presents the US prevalence proportions by age, race/ethnicity and sex (SEER 2015).

Table 2-8 Estimated prevalence proportions (per 10,000 population) on 01 Jan 2012, of the SEER population diagnosed in the previous 20 years

By Age at Prevalence, Race/Ethnicity and Sex												
Race/ Ethnicity	Sex	Age Specific (Crude)										Age-Adjusted [f]
		All Ages	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80+	All Ages
All Races [c]	M+F	1.78	2.73	5.16	2.97	0.80	0.51	0.40	0.43	0.38	0.22	1.84
	M	2.03	2.87	5.70	3.31	1.03	0.56	0.45	0.45	0.39	0.31	2.03
	F	1.54	2.59	4.60	2.60	0.58	0.46	0.36	0.41	0.36	0.17	1.64
White [c]	M+F	2.01	3.09	6.00	3.45	0.98	0.55	0.44	0.46	0.39	0.20	2.11
	M	2.26	3.18	6.57	3.82	1.25	0.61	0.50	0.49	0.42	0.25	2.32
	F	1.77	3.00	5.40	3.06	0.69	0.49	0.39	0.44	0.36	0.18	1.90
Black [c]	M+F	0.90	1.24	2.04	1.58	0.32	0.28	0.21	0.24	-	-	0.83
	M	1.0	1.56	2.37	1.79	0.35	0.28	-	-	-	-	0.94

	F	0.75	0.90	1.70	1.38	0.30	0.27	0.31	0.24	-	-	0.72
Asian/	M+F	1.28	2.27	3.96	1.89	0.45	0.45	0.30	0.30	0.43	0.28	1.39
Pacific	M	1.52	2.52	4.43	2.27	0.53	0.48	0.40	0.31	-	0.74	1.57
Islander [c]	F	1.05	2.01	3.47	1.51	0.38	0.42	0.20	0.29	0.57	-	1.20
	M+F	2.57	3.07	6.07	3.39	1.01	0.71	0.68	0.69	0.76	-	2.20
Hispanic [d]	M	2.90	3.34	6.51	3.96	1.30	0.83	0.79	0.57	-	-	2.42
	F	2.24	2.78	5.61	2.75	0.69	0.59	0.58	0.78	1.05	-	1.95

[c] Statistics based on SEER 11 Areas and Rural Georgia

[d] Statistics based on NHIA for Hispanic for SEER 11 Areas and Rural Georgia

[f] Percentages are age-adjusted to the 2000 US Standard Population (19 age groups - Census P25-1130) by 5-year age groups

Cancer Research UK (CRUK) lists the following risk factors for ALL (Ph+ and Ph- ALL) in general: radiation exposure, exposure to benzene, smoking and coffee drinking, genetic conditions (Down's syndrome, Fanconi anemia, ataxia telangiectasia), past chemotherapy, being overweight, paint exposure and weakened immunity (CRUK 2013).

The main existing treatment options

Current treatment of Ph+ ALL includes imatinib or other TKI inhibitors, combination chemotherapy (cyclophosphamide, vincristine, and doxorubicin), steroids, allogeneic hematopoietic stem-cell transplantation (allo-HSCT) (Ribera 2013). Autologous HSCT may be offered in the absence of a suitable donor or to patients considered unable to undergo allo-HSCT for advanced age or other medical contraindications (Maino et al 2014, Chalandon et al 2015).

Natural history of the indicated condition in the population, including mortality and morbidity

Ph+ ALL is the subgroup of ALL that is associated with the worst prognosis. In 2002, Dombret et al reported long-term survival rates ranging from 35% to 40% in children and less than 20% in adults (Dombret et al 2002).

The introduction of imatinib has improved survival in children and, to lesser extent, in adults with Ph+ ALL. The early results of Children's Oncology Group trial AALL0031 have shown 88% 3-year event-free survival for Ph+ALL patients treated with intensive chemotherapy plus continuous-dosing imatinib (Schultz et al 2010). Hunger et al (2012) reported five year survival rates from the Children's Oncology Group as increasing from 83.7% in 1990-1994 to 90.4% in 2000-2005 (P<0.001).

In 2012, Thyagu et al reported findings from a study of 32 adults with Ph+ ALL treated with imatinib combined with a pediatric-based protocol. Median and 3-year overall survival was 40.7 months and 53%, respectively (Thyagu et al 2012). In 30 prospective studies with patients that were Ph+ ALL, in which 29 of the studies administered imatinib, CR rates ranged from 56% to 100%, with CR rates exceeding 80% in 28 studies. Median DFS ranged from 10 months to 20 months, and median OS ranged from 20-40 months (Couban et al 2014).

Important co-morbidities

Thrombosis is a well-recognized complication of ALL and associated treatment of ALL in both adults and children. Although less frequent than infections, bleeding or gut toxicity, it is among the more frequent serious adverse events (SAEs) reported in trials of ALL therapy. The reported incidence varies from 1% to 36%, depending on the chemotherapy protocol and whether the reported cases are symptomatic or detected on screening radiography (Payne and Vora 2007). Other comorbidities identified in a cohort of Medicare beneficiaries in the US with a primary diagnosis of ALL included septicemia, mycoses, psychoses, depressive disorder, other disorders of the central and peripheral nervous systems, epilepsy/ seizures, hypertension, heart failure, pneumonia, emphysema and acute and chronic kidney disease (Cetin et al 2013).

2.3 Indication: Gastrointestinal Stromal Tumors (GIST)

Incidence

GIST is recognized as a distinct cancer. Prior to 2001, when the specific histology code was introduced, different algorithms were used to identify GIST cases in epidemiologic studies. Differences in methods of case ascertainment contributed to variation in epidemiological findings.

A review of GIST epidemiology by Reddy et al (2007) presents data from four European countries as well as from the US and Taiwan. The incidence has been reported to be (per million): 11 in Iceland, 13 in Italy, 12.7 in the Netherlands, 14.5 in Sweden, 6.8 in the US and 13.7 in Taiwan. In Germany, the crude incidence of GIST in 2013 was estimated to be 21 per million in males and 17 per million in females (incidence of 15 and 11 per million in males and females when age-adjusted to the European population) in 2013 (Ressing et al 2018). Based on the SEER Program data including 6142 GIST patients, the annual age-adjusted US incidence of GIST rose from 5.5/1000000 in 2001 to 7.8/1000000 in 2011 (Ma et al 2014). The overall incidence of GIST from 2001 to 2015 in the US was 7 per million per year, based on data from the United States Cancer Statistics (Patel et al 2019).

Prevalence

Little information has been published on the prevalence of GIST. One recent study of UK patients that failed the first and second line of treatments reported an estimated prevalence of third-line treatment-eligible GIST patients at 10/1000000 (Amelio et al 2014). The review by Reddy et al (2007) mentioned above reported that there were 129 GIST cases per million inhabitants in Sweden (Reddy et al 2007). Based on the SEER program data from 1993 to 2002, Rubin et al (2011) reported 15-year limited-duration prevalence of 16.2 per million.

Demographics of the population in the authorized indication – age, sex, racial and/or ethnic origin and risk factors for the disease

Based on the US SEER Program data (Ma et al 2014), the GIST incidence increases with age, peaking among 70- to 79-year-olds (30.6/1000000). The disease is more common in males than females [incidence rate ratio (RR), 1.35], non-Hispanics than Hispanics (RR, 1.23), and blacks (RR, 2.07) or Asians/Pacific Islanders (RR, 1.50) than whites.

Table 2-9 Age-adjusted incidence of GIST stratified by demographic characteristics and tumor site in the SEER program, 2001–2011

Characteristics	Incidence rate per 1000000 (95% CI)
All	6.78 (6.61 – 6.95)
Age at diagnosis	
8–20	0.11 (0.08 – 0.16)
20–29	0.59 (0.46 – 0.74)
30–39	1.94 (1.70 – 2.19)
40–49	5.35 (4.97 – 5.75)
50–59	11.18 (10.58 – 11.81)
60–69	21.89 (20.81 – 23.01)
70–79	30.64 (29.06–32.29)
80–101	27.18 (25.34–29.12)
Sex	
Male	7.90 (7.63 – 8.18)
Female	5.85 (5.64 – 6.07)
Race	
White	5.92 (5.75 – 6.10)
Black	12.24 (11.50 – 13.01)
American Indian/Alaska Native	2.33 (1.33 – 3.74)
Asian or Pacific Islander	8.89 (8.23 – 9.59)
Ethnicity	
Non-Hispanic white	6.95 (6.76 – 7.13)
Hispanic/Latino	5.65 (5.18 – 6.15)

Source: Ma et al 2014.

Risk factors for GIST include age (the incidence increases sharply with age) and certain genetic syndromes (although most GISTs are sporadic, they may occur in patients with familial GIST syndrome, neurofibromatosis type-1, or -Stratakis syndrome) (Rajendra et al 2013).

The main existing treatment options:

For localized primary GISTs, surgical resection is the mainstay of therapy; adjuvant imatinib is approved for patients with a substantial risk of relapse. Imatinib is approved for the treatment of unresectable metastatic or recurrent GIST. Sunitinib is approved as a second-line therapy following progression on imatinib. Regorafenib is approved to treat patients with advanced GIST that cannot be surgically removed and no longer respond to imatinib and sunitinib.

Natural history of the indicated condition in the population, including mortality and morbidity

Based on the US SEER Program data on 6142 GIST patients diagnosed between 2001 and 2011, Ma et al (2014) reported the median age at diagnosis of 64 years with the range of 8 to 101 years. The most common tumor sites were the stomach (55%) and small intestine (29%). The 5-year overall survival rates were 77%, 64%, and 41% for those with localized, regional, and metastatic disease at diagnosis, respectively. Older age at diagnosis, male sex, black race, and advanced stage at diagnosis were independent risk factors for worse overall survival. In a sample of 430 inoperable/metastatic GIST patients treated with imatinib, median progression free survival was 37.5 months. Median overall survival was 5.8 years; and 8-year over survival rate was 43% (Rutkowski et al 2013).

Important co-morbidities:

Small GISTs (2 cm or less) are usually asymptomatic. Clinical signs and symptoms (nausea, vomiting, abdominal pain, obstruction, abdominal mass, anemia and melena) are non-specific. About 50% of GISTs are overtly metastatic at presentation, with the most common sites of metastases being the peritoneum and the liver. Multiple familial GISTs may be associated with cutaneous hyperpigmentation (Connolly et al 2003). Among 288 patients with GIST analyzed by Nilsson et al (2005), 199 (69%) were detected due to symptoms. Sixty tumors (21%) were detected incidentally during surgery for other reasons, including 32 identified at surgery for other intra-abdominal malignancies, such as colorectal carcinoma (15 tumors), gastric carcinoma (6 tumors), gynecologic cancers (2 tumors), and urinary tract carcinoma.

3 Part II Safety specification Module SII: Non-clinical part of the safety specification

All non-clinical safety findings considered to be of potential clinical relevance have been addressed in the clinical studies and are presented in Section 8.

No additional non-clinical data are required.

Table 3-1 Key safety findings from non-clinical studies and relevance to human usage:

Key Safety findings (from non-clinical studies)	Relevance to human usage
Carcinogenicity	
In the two-year carcinogenicity study in rats receiving doses of 15, 30 and 60 mg/kg/day of imatinib renal adenomas / carcinomas, urinary bladder and urethra papillomas, papillomas / carcinomas of the preputial and clitoral gland, small intestine adenocarcinomas, parathyroid gland adenomas, benign and malignant medullary tumors of the adrenal glands and non-glandular stomach papillomas/carcinomas were identified. The neoplastic changes in the kidney, urinary bladder, urethra, small intestine, parathyroid glands, adrenal glands and non-glandular stomach were noted only at 60 mg/kg/day (approximately 1.74 to 4.14x human daily exposure to imatinib dose of 400 mg/day, based on AUC). The papilloma/carcinoma of the preputial/clitoral gland was noted at 30 and 60 mg/kg/day (approximately 0.5 to 1.7x human daily exposure to imatinib dose of 400 mg/day, based on AUC). The no-effect levels for the various target organs with neoplastic lesions were 30 mg/kg/day for kidney and urinary bladder, urethra, small intestine, parathyroid glands, adrenal glands and non-glandular stomach and 15 mg/kg/day for preputial and clitoral gland. [Study 0210027]	Following the data from pre-clinical studies, 2-yearly updates of the frequency of second primary malignancies (SPM) in imatinib treated patients in Novartis sponsored clinical trials were developed. Overall, the analysis of the safety data from the Novartis sponsored clinical trials does not provide evidence for an increased incidence of malignancies in imatinib treated patients, and specifically for malignancies of bladder, kidney, prostate, oral cavity and pharynx, or lymphoma when compared to the general population also taking into account the potential for an increased risk of developing new malignancy in cancer survivors and others limitations. Second primary malignancy represents an important potential risk for imatinib in RMP version 13.0. For further details please refer to Section 8.3
Gastro intestinal (GI) toxicity	
Diarrhea was observed in the dog at oral doses ≥ 3 mg/kg/day. Emesis was observed at oral doses of ≥ 30 mg/kg in the dog and ≥ 75 mg/kg in the monkey. Atrophy of the intestinal mucosa, vacuolar degeneration of the GI epithelium and single cell necrosis were observed at doses ≥ 10 mg/kg in the dog and at 600 mg/kg in the rat. Diarrhea can most probably be related to the histopathological changes of the GI tract observed. Emesis may be related to a local irritation of the gastric mucosa, since it was not observed in the i.v. studies. [Dog studies: 966024, 001045, 966105]; [Monkey studies 987003, 007019, 007048]; [Rat study: 966023]	Gastro-intestinal hemorrhage and GI obstruction, perforation, or ulceration have been also observed in clinical trials. The risk is adequately communicated through the current SmPC.
Bone changes:	
In the 26-week toxicity study in rats [Study 007033], new bone formation in the tibia, femur and/or in the	The relevance of pre-clinical findings to human usage is not known.

Key Safety findings (from non-clinical studies)	Relevance to human usage
sternum was observed in a dose dependent manner. Similar observations were made in the 2-year rat carcinogenicity study [Study 0210027].	
Reproductive toxicity In rats, doses ≥ 100 mg/kg induced embryo-fetal toxicity and/or teratogenicity (exencephaly, encephalocele, absent or reduced frontal, parietal and/or interparietal skull bones, protruded tongue) in surviving fetuses. Although testes and epididymal weights and percent motile sperm were decreased in male rats at 60 mg/kg dose, there were no effects on mating or on the number of pregnant females. Imatinib is considered embryo-lethal at high doses because of an increased post-implantation loss observed in the fertility study with treatment of both males and females, and in the embryo-toxicity study with the treatment of females. In a pre- and post-natal development study in female rats red vaginal discharge was noted on either gestational Day 14 or 15. In the first generation offspring mean body weights were reduced from birth until terminal sacrifice. First generation offspring fertility was not affected but reproductive effects were noted (increased number of resorptions and decreased number of viable fetuses). No new target organs were identified in the rat juvenile development toxicology study (day 10 to 70 post-partum). In the juvenile toxicology study, transitory effects upon growth and delay in vaginal opening and preputial separation were observed at approximately 0.3 to 2 times the average pediatric exposure at the highest recommended dose of 340 mg/m^2. Also, mortality was observed in juvenile animals (around weaning phase) at approximately 2-times the average pediatric exposure at the highest recommended dose of 340 mg/m^2. [Studies: 974046, 966086, 966088, 017021, 1070428]	Exposure to imatinib during pregnancy might result in an increased risk of fetal abnormalities or spontaneous abortion. Additional details are provided in the important potential risk of tolerability during pregnancy and pregnancy outcomes in Section 8.3.
Hematologic toxicity Repeat-dose toxicity studies have been conducted in rats (up to 26 weeks, by oral gavage), dogs (up to 13 weeks, by capsule) and monkeys (up to 39 weeks, by oral gavage). Mild to moderate hematologic changes were observed in the three species at oral doses ≥ 20, 10 and 75 mg/kg, respectively. Red blood cells were generally affected at doses slightly lower than those causing decreases in WBCs. Minimal to moderate decreases in hemoglobin, hematocrit and minimal to moderate increases in mean cell volume, mean cell hemoglobin, and mean cell hemoglobin concentration were observed beginning at week 7 at doses ≥ 30 mg/kg/day in the 39-week monkey study. The effects persisted at 80 mg/kg/day throughout treatment	Thrombocytopenia, neutropenia and anemia were among the most frequently reported grade 3 and 4 laboratory abnormalities in CML patients. Myelosuppression including cytopenias, thrombocytopenia, neutropenia and anemia is adequately communicated through the current SmPC.

Key Safety findings (from non-clinical studies)	Relevance to human usage
but showed a tendency to return to baseline in animals at 30 mg/kg/day during week 31. [Dog studies: 966024, 001045, 966105]; [Monkey studies 977090, 987003, 007019, 007048]; [Rat studies: 966023, 0110023, 966106, 987004, 0110053, 007033].	
Liver toxicity The liver was a target organ in rats and dogs. Increased transaminases, and decreases in cholesterol, triglycerides, total protein, and albumin were observed in both species. No histopathological changes were seen in rat liver. Liver toxicity in dogs was reflected by microscopic findings consisting of mild multifocal hepatocellular necrosis (single cell type) and single cell necrosis in bile ducts with reactive hyperplasia, and/or inflammation adjacent to blood vessels and bile ducts at doses ≥ 10 mg/kg. After the recovery period, the bile duct hyperplasia progressed in individual animals and was associated with peribiliary fibrosis. An increase in anti-nucleolar antibodies in hepatocytes and epithelial bile duct cells were detected in a 4-week dog exploratory study, the significance of which is currently unclear. [Dog studies: 966024, 001045, 966105]; [Rat studies: 966023, 0110023, 966106, 987004, 0110053, 007033]	Hepatotoxicity is communicated well through the current SmPC.
Renal toxicity The kidney was a target organ in rats and monkeys. In rats, hyperplasia of the transitional epithelium in the renal papilla and of the urinary bladder was observed at doses ≥ 6 mg/kg without changes in serum or urinary parameters. These findings may reflect local irritation of the compound to the urinary tract, since it was shown to be a moderate local irritant after iv administration. In monkeys, focal mineralization and dilatation of renal tubules, and tubular nephrosis were observed in a 2-week oral dose range finding study at 150→100 mg/kg. Biochemical changes indicating renal dysfunction (increased blood urea nitrogen (BUN), creatinine and electrolyte changes) were noted. In the 39-week study, similar microscopic renal changes either involved only individual nephrons or, in the animal that was euthanized early, involved very small portions of the renal parenchyma. Hence these changes had little biological significance. [Monkey studies 977090, 987003, 007019, 007048]; [Rat studies: 966023, 0110023, 966106, 987004, 0110053, 007033]	Imatinib may cause acute renal failure in patients with fluid retention. Acute renal failure is communicated well through the current SmPC.
Safety pharmacology No effect on vital functions involving the cardiovascular, renal or GI systems was observed. No ECG changes were seen after single oral doses of 100 mg in dogs or	The available non-clinical data do not suggest a potential risk of dysrhythmia in humans.

Key Safety findings (from non-clinical studies)	Relevance to human usage
in dogs and monkeys after daily doses of 50 mg/kg up to 13 weeks. hERG and Purkinje assays were not done. [Studies BS117, 606205, BS30, DP00-R07, 001091, 966105, 007048]	
Additional cardiac safety Data from in vitro studies showed that cytotoxic concentrations of imatinib (≥ 10 µM) are required to trigger activation of the endoplasmic reticulum stress response, collapse of the mitochondrial membrane potential, reduction in cellular adenosine triphosphate (ATP) content, and cell death in neonatal rat ventricular myocytes. Similar changes were also observed in heart, lung and skin fibroblasts (primary culture) in vitro indicating lack of specificity for cardiomyocytes. Data from the 4- and 5- weeks mice exploratory studies (ip or oral route of administration) did not reveal any increased heart weight or morphological changes, or effects on the left ventricular structure or function. The results from a 4-week exploratory study in rats demonstrated increased heart weights and myocardial hypertrophy. Electron microscopic evaluation revealed the occurrence of myeloid bodies in endothelial cells, Schwann cells and macrophages of heart and skeletal muscle. These heart effects seen in the rat study concurred with those reported in the 2-year rat carcinogenicity study. There are several concomitant pathologies that may be contributing to the myocardial hypertrophy seen in rats after long term or high dose treatment (for example, an increase in alveolar macrophages, nephrotoxicity and anemia). In the in vivo studies, the imatinib exposures (in terms of Cmax or AUC0-24h) achieved were comparable or higher than those reported for patients at 800 mg/day. [Studies 0670773, 0670541, 0670509, 0770512, RD-2008-50513]	Cardiac disorders are rare or uncommon with imatinib. Cardiac failure is communicated well through the current SmPC.
Mutagenicity In vitro (bacterial and cellular) and in vivo (rat bone marrow micronucleus test) assays were negative. A positive in vitro result was obtained in the chromosome aberration assay at the highest concentration (cytotoxic) tested with metabolic activation. [Studies 956104, 956106, 956105, 966052, 956107]	Non-clinical data do not suggest a potential risk of mutagenicity in humans.

4 Part II Safety specification Module SIII Clinical trial exposure

4.1 Part II Module SIII Clinical trial exposure

The data presented below are only for Glivec (Novartis specific data).

Duration of clinical trial exposure is presented below by indication and overall, by subgroups, age, sex, and race. No data are available for the following special populations: pregnant women, lactating women, cardiac impairment, or subpopulations with genetic polymorphism.

The patient population in the Ph+ ALL indication is based on two co-operative group studies (92 Ph+ patients in Study CSTI571I2301 and 159 Ph+ patients in Study CSTI571AIT07). Details of these two studies are provided in bullets below. Pooling of safety data from these two studies for combined safety analysis was not possible or was not considered appropriate since these two studies have substantial differences in study design and patient population, as well as different doses and duration of imatinib treatment. In addition, raw data sets for both the studies were not available in case pooling would have been appropriate.

- Study CSTI571I2301 (hereafter referred as I2301) - This study enrolled pediatric and young adolescent patients with very high risk (VHR) ALL who were treated with intensive chemotherapy and potentially HSCT with human leukocyte antigen (HLA)-matched related donors. The Ph+ALL patients (n=92) received imatinib (at a dose of 340 mg/m^2/day, reduced to 230 mg/m^2/day in the event of toxicities) in combination with intensive chemotherapy while Ph- patients (n=65) received intensive chemotherapy alone (no imatinib).
- Study CSTI571AIT07 (hereafter referred to as AIT07) - A total of 159 Ph+ ALL pediatric patients (age range of 1.5 to 17.9 years) were evaluated for safety in this study. A total of 128 patients (58 Good risk [i.e. good prognosis]; 70 Poor risk [i.e. poor prognosis]) received imatinib in addition to chemotherapy during the study. Thirty-one patients in the good risk strata did not receive imatinib (as they were randomized to the no imatinib arm). In this study, imatinib was administered at a dose of 300 mg/m^2/day, for a planned total duration of 126 days, but the actual imatinib duration (start and end dates per treatment block in the study duration) was not captured in the database. Hence for this study, clinical trial exposure (Table 4-4) is presented in terms of chemotherapy exposure for patients that received imatinib with chemotherapy.

Table 4-1 Duration of exposure

	CML					ALL		GIST			
	Chronic				Advanced			Metastatic	Adjuvant		
	Adult			Pediatric		Pediatric	Adult		STI571BUS89 1 year Glivec	STI571BFI03 1 and 3 year Glivec	Overall Total (all indications)
Duration	400mg N=1879 n (%)	800mg N=316 n (%)	Total N=2195 n (%)	N=15 n (%)	N=495 n (%)	N=9 n (%)	N=48 n (%)	N=463 n (%)	N=337 n (%)	N=392 n (%)	N=3954 n (%)
Less than 1 year	196 (10.4)	38 (12.0)	234 (10.7)	10 (66.7)	297 (60.0)	9 (100)	46 (95.8)	137 (29.6)	282 (83.7)	114 (29.1)	1129 (28.6)
at least 1 year	1683 (89.6)	278 (88.0)	1961 (89.3)	5 (33.3)	198 (40.0)	0	2 (4.2)	326 (70.4)	55 (16.3)	278 (70.9)	2825 (71.4)
at least 2 years	1494 (79.5)	238 (75.3)	1732 (78.9)	1 (6.7)	132 (26.7)	0	2 (4.2)	206 (44.5)	0	151 (38.5)	2224 (56.2)
at least 3 years	976 (51.9)	221 (69.9)	1197 (54.5)	0	0	0	0	69 (14.9)	0	87 (22.2)	1353 (34.2)
at least 4 years	772 (41.1)	109 (34.5)	881 (40.1)	0	0	0	0	2 (0.4)	0	0	883 (22.3)
at least 5 years	439 (23.4)	0	439 (20.0)	0	0	0	0	0	0	0	439 (11.1)
at least 6 years	131 (7.0)	0	131 (6.0)	0	0	0	0	0	0	0	131 (3.3)
at least 7 years	122 (6.5)	0	122 (5.6)	0	0	0	0	0	0	0	122 (3.1)
at least 8 years	116 (6.2)	0	116 (5.3)	0	0	0	0	0	0	0	116 (2.9)
at least 9 years	110 (5.9)	0	110 (5.0)	0	0	0	0	0	0	0	110 (2.8)

	CML					ALL		GIST			
	Chronic				Advanced			Metastatic	Adjuvant		
	Adult			Pediatric		Pediatric	Adult		STI571BUS89 1 year Glivec	STI571BFI03 1 and 3 year Glivec	Overall Total (all indications)
Duration	400mg N=1879 n (%)	800mg N=316 n (%)	Total N=2195 n (%)	N=15 n (%)	N=495 n (%)	N=9 n (%)	N=48 n (%)	N=463 n (%)	N=337 n (%)	N=392 n (%)	N=3954 n (%)
at least 10 years	90 (4.8)	0	90 (4.1)	0	0	0	0	0	0	0	90 (2.3)
at least 11 years	2 (0.1)	0	2 (0.1)	0	0	0	0	0	0	0	2 (0.1)
Subject-time (years)	6801.4	1004.1	7805.5	12.1	510.5	2.5	15.0	832.8	233.7	649.4	10061.6

Duration of exposure is from first day of treatment to last day of treatment.
Subject-time is the sum of each subject's treatment exposure in years.
Source: [EU RMP version 13.0 Annex-7 Table-1.1]

Table 4-2 Clinical trial exposure – Rare disease indications

Exposure (months)	DFSP N=12	HES N=14	MPD N=7	SM N=5
Mean ±SD	10.3 ±10.3	11.5 ±10.1	15.2 ±12.0	10.3 ±9.1
Median	6.2	8.8	23.6	12.5
Minimum-Maximum	0.1 – 30.4	0.5 – 23.3	0.8 – 26.7	1.1 – 22.3

Source: Study STI571B2225

Pediatric Ph+ ALL patient exposure:

I2301: N=92 Ph+ ALL and N=65 Ph- (who did not receive imatinib) - The 92 Ph+ ALL patients were enrolled in Cohorts 1 to 5 in non-randomized sequential fashion that incorporated imatinib both earlier in the course of treatment and during more treatment blocks from Cohort 1 to Cohort 5 (Cohort 5 patients received continuous imatinib dosing from start of study to maintenance therapy). Of the 92 Ph+ ALL patients, 58 patients received imatinib in combination with chemotherapy (no HSCT), 21 patients received imatinib and HSCT, and 13 patients received imatinib in the off protocol HSCT group. Per protocol HSCT included patients transplanted with a matched-related donor, the other transplanted patients were considered off protocol (Table 4-3).

AIT07: N=90 in good risk (N=58 plus imatinib, N=31 no imatinib), N=70 in poor risk plus imatinib (actual). Overall, 128 patients received imatinib plus chemotherapy in this study (58 patients from good risk and 70 patients from poor risk) (Table 4-4).

Table 4-3 Clinical trial exposure – pediatric patients with ALL in Study I2301

	Overall exposure (days) to imatinib, chemotherapy + imatinib group (no HSCT)					
	Cohort 1 N=5	**Cohort 2 N=9**	**Cohort 3 N=8**	**Cohort 4 N=6**	**Cohort 5 N=30**	**All Ph+ N=58**
Exposure (days)						
n	3	9	8	6	30	56
Mean	148.7	306.8	345.4	297.7	586.2	452.5
SD	96.93	193.61	157.83	221.62	273.55	274.64
Minimum	41	12	91	58	62	12
Median	176.0	387.0	401.5	249.5	708.0	465.0
Maximum	229	498	493	577	867	867

	Overall exposure (days) to imatinib, per protocol HSCT group											
	Cohort 1 N=2		**Cohort 2 N=1**		**Cohort 3 N=1**		**Cohort 4 N=4**		**Cohort 5 N=13**		**All Ph+ N=21**	
	Pre-HSCT	**Post HSCT**	**Pre-HSCT**	**Post HSCT**	**Pre-HSCT**	**Post HSCT**	**Pre-HSCT**	**Post HSCT**	**Pre-HSCT**	**Post HSCT**	**Pre-HSCT**	**Post HSCT**
n	0	1	1	1	1	1	4	4	13	12	19	19
Mean		168	21	169	42	188	44.3	135.8	46.5	149	44.5	150.3

SD	-	-	-	-	-	8.54	81.92	9.92	61.3	10.57	59.82
Minimum	168	21	169	42	188	39	14	42	17	21	14
Median	168	21	169	42	188	40.5	168.5	42	169	42	169
Maximum	168	21	169	42	188	57	192	77	192	77	192

	Overall exposure (days) to imatinib, off protocol HSCT group					
	Cohort 1	**Cohort 2**	**Cohort 3**	**Cohort 4**	**Cohort 5**	**All Ph+**
	N=0	**N=2**	**N=2**	**N=2**	**N=7**	**N=13**
n	0	2	2	2	7	13
Mean	-	54.5	41.5	52	89.4	70.9
SD	-	17.68	3.54	33.94	50.5	42.98
Minimum	-	42	39	28	42	28
Median	-	54.5	41.5	52	63	53
Maximum	-	67	44	76	165	165

For Ph+ ALL patients, duration of imatinib exposure was calculated as the sum of the time from start to end of imatinib treatment per block. Imatinib-free treatment blocks were not included. For Ph- patients, duration of chemotherapy was calculated as the sum of all time from start to end of each chemotherapy treatment block.

Source: Study I2301-Table 14.3-1.3, Study I2301-Table 14.3-1.5, and Study I2301-Table 14.3-1.7

Table 4-4 Clinical trial exposure – pediatric ALL patients in Study AIT07

	AIT07			
	Good risk		**Poor risk**	**All imatinib**
	No imatinib	**Plus imatinib**	**Plus imatinib**	
	N=31	**N=58**	**N=70**	**N=128**
Exposure (days)				
n	27(87.1)	53 (91.4)	61 (87.1)	114 (89.1)
Mean	114.3	123.2	121.5	122.3
SD	15.6	17.3	13.7	15.4
Minimum	90	86	81	81

	AIT07			
	Good risk		Poor risk	All imatinib
	No imatinib	Plus imatinib	Plus imatinib	
	N=31	N=58	N=70	N=128
Median	112	121	120	120
Maximum	145	169	152	169

Exposure to chemotherapy is presented, and calculated (in days) from start to end date of consolidation 3, for patients who actually entered each phase
Source: Study AIT07-Table 14.3-2.4

Table 4-5 Exposure by age group and sex (CML indication)

		CML									
		Chronic CML								Advanced CML	
		Adult						Pediatric			
		400g N=1879		800g N=316		Total N=2195		N=15		N=495	
Age	Sex	Subjects n (%)	Subject-time (years)	Subjects n (%)	Subject-time (years)	Subjects n (%)	Subject-time (years)	Subjects n (%)	Subject-time (years)	Subjects n (%)	Subject-time (years)
Total	Total	1879 (100)	6801.4	316 (100)	1004.1	2195 (100)	7805.5	15 (100)	12.1	495 (100)	510.5
	Male	1099 (58.5)	3963.4	181 (57.3)	600.5	1280 (58.3)	4564.0	8 (53.3)	5.7	254 (51.3)	239.3
	Female	780 (41.5)	2838.0	135 (42.7)	403.6	915 (41.7)	3241.5	7 (46.7)	6.4	241 (48.7)	271.2
< 18 years	Total	0		0		0		12 (80.0)	8.9	0	
	Male	0		0		0		7 (46.7)	4.4	0	
	Female	0		0		0		5 (33.3)	4.6	0	
≥ 18 - < 65 years	Total	1613 (85.8)	5944.0	263 (83.2)	855.7	1876 (85.5)	6799.7	3 (20.0)	3.2	372 (75.2)	371.6
	Male	949 (50.5)	3507.4	148 (46.8)	506.2	1097 (50.0)	4013.6	1 (6.7)	1.4	190 (38.4)	170.0
	Female	664 (35.3)	2436.6	115 (36.4)	349.5	779 (35.5)	2786.1	2 (13.3)	1.8	182 (36.8)	201.7

≥ 65 years	Total	266 (14.2)	857.4	53 (16.8)	148.4	319 (14.5)	1005.8	0	123 (24.8)	138.9
	Male	150 (8.0)	456.0	33 (10.4)	94.3	183 (8.3)	550.4	0	64 (12.9)	69.3
	Female	116 (6.2)	401.4	20 (6.3)	54.1	136 (6.2)	455.4	0	59 (11.9)	69.5

Subject-time is the sum of each subject's treatment exposure in years.
Subject-time is based on the number of subjects in each category.
Source: [EU RMP version 13.0 Annex 7 – Table 1.2]

Table 4-6 Exposure by age group and sex (ALL, GIST and all indications)

		ALL				GIST							
						Metastatic		Adjuvant					
		Pediatric N=9		Adult N=48		N=463		STI571BUS89 1-year Glivec N=337		STI571BFI03 1 and 3-year Glivec N=392		Overall Total (All Indications) N=3954	
Age	Sex	Subjects n (%)	Subject-time (years)	Subjects n (%)	Subject-time (years)	Subjects n (%)	Subject-time (years)	Subjects n (%)	Subject-time (years)	Subjects n (%)	Subject-time (years)	Subjects n (%)	Subject-time (years)
Total	Total	9 (100)	2.5	48 (100)	15.0	463 (100)	832.8	337 (100)	233.7	392 (100)	649.4	3954 (100)	10062
	Male	9 (100)	2.5	24 (50.0)	6.2	269 (58.1)	460.6	160 (47.5)	112.4	199 (50.8)	345.8	2203 (55.7)	5736.6
	Female	0		24 (50.0)	8.9	194 (41.9)	372.2	177 (52.5)	121.3	193 (49.2)	303.6	1751 (44.3)	4325.1
< 18 years	Total	9 (100)	2.5	0		0		0		0		21 (0.5)	11.5
	Male	9 (100)	2.5	0		0		0		0		16 (0.4)	6.9
	Female	0		0		0		0		0		5 (0.1)	4.6
≥ 18 - < 65 years	Total	0		44 (91.7)	13.4	342 (73.9)	630.3	229 (68.0)	172.1	240 (61.2)	424.0	3106 (78.6)	8414.3
	Male	0		21 (43.8)	4.7	206 (44.5)	370.3	110 (32.6)	79.7	121 (30.9)	222.1	1746 (44.2)	4861.8
	Female	0		23 (47.9)	8.7	136 (29.4)	259.9	119 (35.3)	92.4	119 (30.4)	202.0	1360 (34.4)	3552.5
≥ 65 years	Total	0		4 (8.3)	1.6	121 (26.1)	202.6	108 (32.0)	61.6	152 (38.8)	225.4	827 (20.9)	1635.8
	Male	0		3 (6.3)	1.5	63 (13.6)	90.3	50 (14.8)	32.7	78 (19.9)	123.7	441 (11.2)	867.9

	Female	0	1 (2.1)	0.1	58 (12.5)	112.3	58 (17.2)	28.9	74 (18.9)	101.7	386 (9.8)	768.0

Subject-time is the sum of each subject's treatment exposure in years.
Subject-time is based on the number of subjects in each category.
Source: [EU RMP version 13.0 Annex 7 – Table 1.2]

Table 4-7 Exposure by race (CML indication)

	CML									
	Chronic CML								Advanced CML	
	Adult						Pediatric			
	400g N=1879		800g N=316		Total N=2195		N=15		N=495	
Race	Subjects n (%)	Subject-time (years)	Subjects n (%)	Subject-time (years)	Subjects n (%)	Subject-time (years)	Subjects n (%)	Subject-time (years)	Subjects n (%)	Subject-time (years)
Total	1879 (100)	6801.4	316 (100)	1004.1	2195 (100)	7805.5	15 (100)	12.1	495 (100)	510.5
Caucasian	1578 (84.0)	5613.1	240 (75.9)	770.3	1818 (82.8)	6383.4	7 (46.7)	6.9	431 (87.1)	463.0
Black	95 (5.1)	283.0	17 (5.4)	51.4	112 (5.1)	334.4	2 (13.3)	1.8	31 (6.3)	22.2
Asian	115 (6.1)	568.0	41 (13.0)	128.9	156 (7.1)	696.9	0		7 (1.4)	2.6
Other	91 (4.8)	337.2	18 (5.7)	53.5	109 (5.0)	390.8	6 (40.0)	3.4	26 (5.3)	22.7
Unknown	0		0		0		0		0	

Subject-time is the sum of each subject's treatment exposure in years.
Subject-time is based on the number of subjects in each category.
Source: [EU RMP version 13.0 Annex 7 – Table 1.3]

Table 4-8 Exposure by race (ALL, GIST and all indications)

	ALL				GIST					
					Metastatic		Adjuvant			
	Pediatric N=9		Adult N=48		N=463		STI571BUS89 (1-year Glivec) N=337		Overall Total (All Indications) N=3562	
Race	Subjects n (%)	Subject-time (years)	Subjects n (%)	Subject-time (years)	Subjects n (%)	Subject-time (years)	Subjects n (%)	Subject-time (years)	Subjects n (%)	Subject-time (years)
Total	9 (100)	2.5	48 (100)	15.0	463 (100)	832.8	337 (100)	233.7	3562 (100)	9412.2
Caucasian	3 (33.3)	1.1	40 (83.3)	12.7	319 (68.9)	576.2	272 (80.7)	191.8	2890 (81.1)	7635.1
Black	1 (11.1)	0.1	3 (6.3)	1.0	15 (3.2)	21.4	38 (11.3)	24.1	202 (5.7)	405.0
Asian	2 (22.2)	0.2	3 (6.3)	0.9	122 (26.3)	220.2	20 (5.9)	12.7	310 (8.7)	933.4
Other	3 (33.3)	1.2	2 (4.2)	0.5	7 (1.5)	15.0	2 (0.6)	1.4	155 (4.4)	434.9
Unknown	0		0		0		5 (1.5)	3.7	5 (0.1)	3.7

Subject-time is the sum of each subject's treatment exposure in years.
Subject-time is based on the number of subjects in each category.
Adjuvant GIST study SSG (BFI03) has no race data and is not presented.
Source: [EU RMP version 13.0 Annex 7 – Table 1.3]

Pediatric Ph+ ALL: In the studies (I2301 and AIT07), exposure by age, sex, and race have not been presented due to limitations in the data collected for these studies. Demographic summaries of these two studies by each cohort/ group have been presented for these studies in the tables below.

Table 4-9 Demographics summary - pediatric ALL patients in Study I2301

	Cohort 1 N=7 n (%)	Cohort 2 N=12 n (%)	Cohort 3 N=11 n (%)	Cohort 4 N=12 n (%)	Cohort 5 N=50 n (%)	All Ph+ N=92 n (%)	Ph- N=65 n (%)
Age-groups for risk classification*							
<10 years	4 (57.1)	6 (50.0)	4 (36.4)	6 (50.0)	26 (52.0)	46 (50)	29 (44.6)

	Cohort 1 N=7 n (%)	Cohort 2 N=12 n (%)	Cohort 3 N=11 n (%)	Cohort 4 N=12 n (%)	Cohort 5 N=50 n (%)	All Ph+ N=92 n (%)	Ph- N=65 n (%)
≥10 years	3 (42.9)	6 (50.0)	7 (63.6)	6 (50.0)	24 (48.0)	46 (50)	36 (55.4)
Age-group per ICH guidelines							
<2 years	0	0	0	0	2 (4.0)	2 (2.2)	-**
2-<12 years	4 (57.1)	8 (66.7)	6 (54.5)	6 (50.0)	28 (56.0)	52 (56.5)	37 (56.9)**
12-<18 years	3 (42.9)	4 (33.3)	4 (36.4)	5 (41.7)	16 (32.0)	32 (34.8)	27 (41.5)
18 years or more	0	0	1 (9.1)	1 (8.3)	4 (8.0)	6 (6.5)	1 (1.5)
Sex							
Male	6 (85.7)	9 (75.0)	5 (45.5)	9 (75.0)	30 (60.0)	59 (64.1)	36 (55.4)
Female	1 (14.3)	3 (25.0)	6 (54.5)	3 (25.0)	20 (40.0)	33 (35.9)	29 (44.6)
Race							
White	6 (85.7)	9 (75.0)	11 (100)	9 (75.0)	34 (68.0)	69 (75)	48 (73.8)
Other	1 (14.3)	3 (25)	0	3 (25)	16 (32)	23 (25)	17 (26.2)

*Because age at study entry was used to evaluate risk classification, instead of age at diagnosis the term “Risk categories” was used, instead of “National Cancer Institute (NCI) risk categories”.

**For the Ph- population only counts for patients in the overall <12 years category are presented since it is not possible to split the age categories into <2 years and 2-<12 years due to the unavailability of data.

Source: Study I2301-Table 14.1-3.1, Study I2301-Addendum Table 14.1-1.2, and Glivec D120 AtoQ

Table 4-10 Demographic summary - pediatric ALL patients in Study AIT07

	Good risk		Poor risk	All with imatinib
	No imatinib N=31 n (%)	Plus imatinib N=58 n (%)	Plus imatinib N=70 n (%)	N=128 n (%)
Baseline age (years)				
N	31	58	70	128
Mean	8.9	8.4	10.3	9.4
SD	4.1	4.9	4.3	4.7
Minimum	1.5	1.6	2	1.6
Q1	6.8	4.1	6.4	5.3
Median	9	7.6	11.1	10
Q3	12.1	12.8	13.8	13.4
Maximum	16.1	17.9	16.8	17.9
Age-groups - risk group				
<10 years	21 (67.7)	35 (60.3)	29 (41.4)	64 (50)
≥10 years	10 (32.3)	23 (39.7)	41 (58.6)	64 (50)
Age-group–according to Pediatric Investigational Plan (PIP)				
<2 years	2 (6.5)	5 (8.6)	0 (0)	5 (3.9)
2-<12 years	21 (67.7)	34 (58.6)	38 (54.3)	72 (56.3)
12-<18 years	8 (25.8)	19 (32.8)	32 (45.7)	51 (39.8)
≥18 years	0 (0)	0 (0)	0 (0)	0 (0)
Sex				
Male	17 (54.8)	40 (69)	44 (62.9)	84 (65.6)
Female	14 (45.2)	18 (31)	26 (37.1)	44 (34.4)

Source: Study AIT07-Table 14.1-1.5

5 Part II Safety specification Module SIV: Populations not studied in clinical trials

The data presented below are only for Glivec (Novartis specific data).

5.1 Part II Module SIV.1 Exclusion criteria in pivotal clinical studies within the development program

Table 5-1 Important exclusion criteria in pivotal studies in the development program

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
Less than 5 years free of another primary malignancy, except basal cell skin cancer and cervical carcinoma in situ	Patients with malignancies have worse prognosis with shorter survival time in general; including them in clinical trials may confound the assessment of efficacy and safety data.	No	No different imatinib safety profile is expected in CML or GIST patients with concomitant other malignancies.
Pregnant or breast-feeding women	There are limited data on the use of imatinib in pregnant women. Studies in animals have however shown reproductive toxicity and the potential risk for the fetus is unknown.	No	This is an important potential risk and is discussed in detail in Section 8.3. This risk is communicated through the SmPC.
Patients with acute or chronic liver disease (chronic active hepatitis, cirrhosis), significant alanine amino transferase (ALT)/ total bilirubin elevation	Imatinib is mainly metabolized through the liver.	No	The use of imatinib in hepatic impairment is considered well characterized based on the data from clinical trials as well as from over 15 years of post-marketing experience and it is considered adequately controlled.
Known human immunodeficiency viruses (HIV) infection	HIV positive patients have been also excluded, because of the possible effect on HIV viral suppression	No	There is currently no experience with imatinib in patients testing positive for HIV.

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
Severe renal disease, creatinine levels more than 2 x the upper limit of normal (ULN)	Imatinib and its metabolites are not significantly excreted via the kidney. As the renal clearance of imatinib is negligible, a decrease in total body clearance is not expected in patients with renal insufficiency.	No	The free drug clearance of imatinib is likely similar between patients with renal impairment and those with normal renal function, since renal excretion represents only a minor elimination pathway for imatinib.
Children below 2 years of age	There is no experience with the use of imatinib in children with CML below 2 years of age and with Ph+ALL below 1 year of age. There is very limited experience in children with other indications.	Yes	Not applicable

5.2 Part II Module SIV.2. Limitations to detect adverse reactions in clinical trial development programs

Rare adverse reactions: Many patients/subjects have received imatinib treatment in Novartis-sponsored investigational clinical trials cumulatively since the Development International Birth date (10-May-2001). Considering the extent and duration of exposure, it is highly unlikely (<0.00625%) to find a rare adverse drug reaction (ADR).

Adverse reactions with a long latency: Long latency adverse drug reactions are defined as ADRs which occur six months or more after initial exposure (Fletcher and Griffin 1991). Based on the review of the safety profile for patients with more than six months of exposure there is no evidence for imatinib induced long latency adverse drug reactions so far.

Adverse reactions due to prolonged exposure: The longest imatinib exposure corresponds to the key pivotal study STI571A0106 (IRIS study) in the approved indication of newly diagnosed CML, which was completed after twelve years of follow-up. Data collected to date do not suggest an adverse reaction due to long-term exposure, and some patients have been exposed to imatinib for approximately fifteen years.

Adverse reactions due to cumulative exposure: Available data come from the key pivotal study STI571A0106 (IRIS study) in the approved indication of newly diagnosed CML. A population PK analysis was performed on Day 1 and Day 29 of therapy in all patients initially randomized to the imatinib treatment arm. Trough level plasma samples on Day 29 (steady state, n=351) showed an overall mean (±SD, CV%) steady state Cmin for imatinib and its metabolite CGP74588 of 979 ng/mL (±530 ng/mL, 54.1%) and 242 ng/mL (±106 ng/mL, 43.6%), respectively (Larson et al 2008). High imatinib plasma exposure may lead to a higher frequency of certain adverse events such as fluid retention, rash, myalgia, and anemia. However, no increase in discontinuation due to adverse events was observed among patients with the highest imatinib exposure, suggesting that adverse events remain manageable.

5.3 Part II Module SIV.3. Limitations in respect to populations typically underrepresented in clinical trial development programs

Table 5-2 Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding women	
Pediatric patients	Refer to Section 4
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Not applicable since the product is in post-marketing.
Population with relevant different racial and/or ethnic origin	Refer to Section 4
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program

6 Part II Safety specification Module SV: Post-authorization experience

6.1 Part II Module SV.1. Post-authorization exposure

6.1.1 Part II Module SV.1.1 Method used to calculate exposure

It is difficult to provide the exact number of patients exposed to a marketed drug. The variability in the approved doses between 400 and 800 mg per day and the lack of information on the use for each indication introduce additional complexities.

For CML the recommended dosage of Glivec is 400 mg daily for patients in chronic phase CML and 600 mg daily for patients in accelerated phase or blast crisis, with increases up to 800 mg daily in patients with disease progression and/or failure to achieve hematological response within three months. The recommended dose for patients with unresectable or metastatic GIST is 400 mg daily with possible dose increase to 600 mg or 800 mg daily in the absence of a sufficient treatment response.

Patient exposure is calculated using the recommended daily dose/ recommended starting daily dose in CML-CP, MDS/ MPD, SM, HES/ CEL and GIST, which is 400 mg daily.

6.1.2 Part II Module SV.1.2. Exposure

An estimate of patient exposure is calculated based on worldwide sales volume in milligrams (mg) of active substance sold and the recommended daily dose/ recommended starting daily dose in CML-CP, MDS/MPD, SM, HES/CEL and GIST, which is 400 mg daily.

The estimated cumulative post-marketing exposure by formulation is provided in Table 6-1 and the estimated cumulative marketing exposure by formulation and region is shown in Table 6-2.

Table 6-1 Estimated cumulative post-marketing exposure until 10-May-2021

Formulation	Cumulative post-marketing exposure until 10-May-2021**	
	Amount sold (mg)	Estimated exposure (PTY)
Novartis Pharma		
Film coated tablet	231,772,365,096	1,587,482
Hard capsule	42,500,758,888	291,101
Sandoz International GmbH		
Film coated tablet	4,229,266,696	28,968
Total	278,502,390,680	1,907,551

PTY: patient treatment years

**Sales data for cumulative period is obtained until 30 Apr 2021.

Source: Glivec PSUR (reporting period 11-May-2018 to 10-May-2021)

Table 6-2 Cumulative exposure from marketing experience in patient treatment years

	EEA	USA and Canada	Japan	ROW	Total
Novartis Pharma		[redacted]			
Film coated tablet	388,413			704,306	1,587,482
Hard capsule	136,969			113,110	291,101
Sandoz International GmBH					
Film coated tablet	19,477			9,490	28,968
Total**	544,425			827,341	1,907,551

EEA: European Economic Area; ROW: Rest of the World (UK and Switzerland included); USA: United States of America.

**Sales data for cumulative period is obtained until 30 Apr 2021.

Source of data: Glivec PSUR (reporting period 11-May-2018 to 10-May-2021); Novartis Worldwide sales volume.

7 Part II Safety specification Module SVI: Additional EU requirements for the safety specification

7.1 Potential for misuse for illegal purposes

Based on the mechanism of action and the preclinical and clinical safety profile, a potential for abuse, dependence or use for illegal purposes is not anticipated.

8 Part II Safety specification Module SVII: Identified and potential risks

8.1 Part II SVII.1. Identification of safety concerns in the initial RMP submission

This section is not applicable as this is not the initial RMP.

8.1.1 Part II SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable

8.1.2 SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable

8.2 Part II SVII.2. New safety concerns and reclassification with a submission of an updated RMP

Changes in RMP v 13.0 compared to RMP v 12.1:

The following safety concern was removed in the current RMP v 13.0.

- Missing information:
  - Pediatric patients: Long term follow up

The study CSTI571I2201 (A European observational registry collecting efficacy and safety data in newly diagnosed pediatric Ph+ ALL patients treated with chemotherapy + imatinib, with or without hematopoietic stem cell treatment [+/- HSCT]) has been completed (LPLV: 01-Sep-2022). The study results didn't reveal any safety finding in long term follow-up of pediatric patients with Ph+ ALL (in this study, long term safety and efficacy data was collected such that the observational follow-up for each patient was a minimum of 5 years from start of imatinib treatment or such available data until early patient discontinuation).

Earlier, study CSTI571A2405 (International Observational Registry for Chronic Myeloid Leukemia Treatment and Outcome in Children and Adolescents) was completed (24-Jan-2017). This study was aimed to evaluate the CML treatment and outcome in children and adolescents' pediatric patients including long-term follow-up relevant to growth and development, as well as sexual development, especially in pediatric patients who were treated with imatinib.

In addition to above studies (analyzing Glivec's safety in pediatric patients after long term follow-up), the topic 'Pediatric patients: long term follow up' has been evaluated over nine years in Glivec PSURs. Review of data in Glivec PSURs didn't reveal any new safety findings regarding long term follow-up in pediatric patients who have received imatinib.

Since the knowledge of long-term use of imatinib has accumulated, and no new safety finding has been observed, the safety concern 'Pediatric patients: Long term follow up' was removed from missing information. The current routine risk minimization activities are found to be adequate to mitigate this risk.

8.3 Part II SVII.3. Details of important identified risks, important potential risks, and missing information

The clinical trial information was recoded to MedDRA version 23.1 for all included studies.

Not each sub-category given in the following risk tables (identified and potential), were available in all studies:

- The relationship to treatment, action taken, and seriousness were not collected in STI571BFI03 (Adjuvant GIST (1 and 3-Year Glivec), N=392).
- Action taken was not collected in STI571 0103 (Chronic CML Pediatric, N=15 and ALL Pediatric, N=9).
- The attributes for "Dose adjustment/interruption" and "Non-drug therapy given" were not collected in study STI571BUS98 (Adjuvant GIST (1-Year Glivec), N=337).
- Therefore, the percentages and 95% CI in the Overall Total (all indications) column for each sub-category are calculated using as total N the number of patients in the studies with the available attributes.
  - All AEs, Grade 3 AEs and Grade 4 (or 5) AEs are based on a total N of 3954.
  - Treatment-related AEs and SAEs are calculated using a total N of 3562 (excluding study STI571BFI03).
  - "Permanently discontinued", "Concomitant medication taken", "Leading to hospitalization" and "None" are based on a total N of only 3538 (excluding studies STI571BFI03 and STI571 0103).
  - "Dose adjustment/interruption" and "Non-drug therapy given" are calculated using a total N of only 3201 (excluding studies STI571BFI03, STI571 0103 and STI571BUS98).

Pediatric Ph+ ALL: A pooled analysis from the studies I2301 and AIT07 was not provided since the data analyses were done in cooperative groups for one study and for part of the second study. Therefore, for all the risks (identified and potential), information from both the pediatric Ph+ ALL studies (I2301 and AIT07) has been manually obtained from individual clinical study reports (CSR). In the I2301 study, control data from the Ph- population has been included in the risk tables, where available. Similarly, in the AIT07 study, control data from the Good risk no imatinib arm has been included in the risk tables, where available.

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8.3.1 SVII.3.1. Presentation of important identified risks and important potential risks

The data presented below are only for Glivec (Novartis specific data).

8.3.1.1 Important identified risks

There are no important identified risks for imatinib.

8.3.1.2 Important potential risk: Second primary malignancy

Table 8-1 Clinical trial data of second primary malignancy

	CML					ALL		GIST			
	Chronic				Advanced			Metastatic	Adjuvant		
	Adult			Pediatric		Pediatric	Adult		STI571BUS89 1 year Glivec	STI571BFI03 1 and 3 year Glivec	Overall Total (all indications))
	400mg N=1879 n (%) 95% CI	800mg N=316 n (%) 95% CI	Total N=2195 n (%) 95% CI	N=15 n (%) 95% CI	N=495 n (%) 95% CI	N=9 n (%) 95% CI	N=48 n (%) 95% CI	N=463 n (%) 95% CI	N=337 n (%) 95% CI	N=392 n (%) 95% CI	N=3954 n (%) 95% CI
Number of subjects with at least one event	144 (7.7) (6.5, 9.0)	23 (7.3) (4.7,10.7)	167 (7.6) (6.5, 8.8)	0 (0.0,21.8)	86 (17.4) (14.1,21.0)	0 (0.0,33.6)	8 (16.7) (7.5,30.2)	20 (4.3) (2.7, 6.6)	6 (1.8) (0.7, 3.8)	3 (0.8) (0.2, 2.2)	290 (7.3) (6.5, 8.2)
Maximum grade											
Grade 3 AEs	36 (1.9)	10 (3.2)	46 (2.1)	0	30 (6.1)	0	2 (4.2)	7 (1.5)	1 (0.3)	0	86 (2.2)
Grade 4 (or 5) AEs	54 (2.9)	8 (2.5)	62 (2.8)	0	37 (7.5)	0	4 (8.3)	8 (1.7)	2 (0.6)	0	113 (2.9)
SAEs*	95 (5.1)	19 (6.0)	114 (5.2)	0	61 (12.3)	0	7 (14.6)	14 (3.0)	1 (0.3)	-	197 (5.5)

Numbers (n) represent counts of subjects.
*Seriousness was not collected in STI571BFI03.
95% CI is derived from the Clopper-Pearson formula.
MedDRA version 23.1
Source: [EU RMP version 13.0 Annex-7 – Table 16.4-4.1]

Table 8-2 Important potential risk of second primary malignancy: other details

Second Primary Malignancy	Details
Potential mechanisms	Pertaining to pre-clinical studies: additional ADME, genotoxicity, and comparative time course studies in rats were performed. Based on data from these studies and the published literature, the neoplastic changes observed in the urogenital tract may be the result of the combination of toxicity and an exaggerated pharmacological effect. The small intestine and non-glandular stomach tumors may be associated to the toxicity on the GI tract. The neoplasia observed in the parathyroid and adrenals may be secondary to direct toxic effect on the kidney and resulting disturbances to calcium homeostasis
Evidence sources and strength of evidence	The severity and nature of an identified malignancy will generally vary with the specific type of malignancy and the promptness with which it is identified and treated. No characteristic pattern has been identified with imatinib. Rebora et al (2010) used the Swedish Cancer Registry to assess the incidence rates of second primary cancers among CML patients. With a total of a 145 subsequent primary malignancies identified in 2,753 adult patients diagnosed with CML between 1970 and 1995, an increased incidence rate of second malignancy was found for all-site cancers (standardized incidence rate – SIR of 1.82, 95%CI: 1.53 – 2.14), stomach cancer (SIR = 2.76, 95%CI: 1.33 – 5.08), skin cancer (SIR = 5.36, 95%CI: 3.18 – 8.47), urogenital tract cancer (SIR = 1.61, 95%CI: 1.15 – 2.21), and lymphoid leukemia (SIR = 5.53, 95%CI: 1.79 – 12.89). Among 856 survivors of childhood ALL, 44 developed second primary neoplasms; 41 of them radiation-related. The risk of a second neoplasm was significantly higher in the 597 patients who received radiation therapy (irradiated group) than in the 259 patients who did not (p=0.04; estimated cumulative risk [+/-SE] at 20 years, 20.9+/-3.9% vs. 0.95+/-0.9%) (Pui et al 2003).
Characterization of the risk:	Novartis has performed a cumulative epidemiologic frequency analysis of second primary malignancies in imatinib treated patients in Novartis sponsored clinical trials since 2004, and the last update of that analysis (the 14th sequential analysis) was done in Dec-2019. The analysis of safety data from the Novartis sponsored clinical trials has provided no evidence for an increased incidence of malignancies overall or specifically malignancies of bladder, kidney, prostate, oral cavity and pharynx, or lymphoma in patients treated with imatinib compared to that of the general population and compared to that of the CML patient population. This conclusion has been consistent since 2004. Pediatric Ph+ALL: No case reports of second primary malignancies have been received from I2301 and AIT07 [Study I2301] and [Study AIT07].

Second Primary Malignancy	Details
	Based on the new information received as of the DLP (10-May-2021) the characterization of the risk does not need an update. The known risk profile remains unaltered and valid. Review of clinical trials data and post-marketing data there is no evidence of an increased incidence of malignancies in imatinib-treated patients when compared to the general population, taking into account the potential for an increased risk of developing new malignancy in cancer survivors. Evaluation of the information received during the PSUR reporting interval and cumulatively does not warrant a change to the characterization of this important identified risk.
Risk factors and risk groups	Unknown
Preventability	Unknown
Impact on the benefit-risk balance of the product	Potentially significant as it may cause psychological as well as physical morbidity and affect the life expectancy. Important risk to consider in assessing benefit-risk. Overall benefit-risk profile of imatinib remains favorable in the approved indications.
Public health impact	The analysis of safety data from the Novartis sponsored clinical trials has not provided evidence for an increased incidence of malignancies overall.

8.3.1.3 Important potential risk: Tolerability during pregnancy and pregnancy outcomes

Table 8-3 Clinical trial data of tolerability during pregnancy and pregnancy outcomes

CML					ALL		GIST			
Chronic				Advanced			Metastatic	Adjuvant		
Adult			Pediatric		Pediatric	Adult		STI571BUS89 1 year Glivec	STI571BFI03 1 and 3 year Glivec	Overall Total (all indications)
400mg N=1879 n (%) 95% CI	800mg N=316 n (%) 95% CI	Total N=2195 n (%) 95% CI	N=15 n (%) 95% CI	N=495 n (%) 95% CI	N=9 n (%) 95% CI	N=48 n (%) 95% CI	N=463 n (%) 95% CI	N=337 n (%) 95% CI	N=392 n (%) 95% CI	N=3954 n (%) 95% CI

Number of subjects with at least one event	45 (2.4) (1.8, 3.2)	10 (3.2) (1.5, 5.7)	55 (2.5) (1.9, 3.2)	0 (0.0,21.8)	4 (0.8) (0.2, 2.1)	0 (0.0,33.6)	0 (0.0, 7.4)	3 (0.6) (0.1, 1.9)	0 (0.0, 1.1)	4 (1.0) (0.3, 2.6)	66 (1.7) (1.3, 2.1)
Maximum grade											
Grade 3 AEs	6 (0.3)	0	6 (0.3)	0	1 (0.2)	0	0	0	0	0	7 (0.2)
Grade 4 (or 5) AEs	4 (0.2)	1 (0.3)	5 (0.2)	0	1 (0.2)	0	0	0	0	0	6 (0.2)
SAEs*	15 (0.8)	5 (1.6)	20 (0.9)	0	3 (0.6)	0	0	1 (0.2)	0	-	24 (0.7)

Numbers (n) represent counts of subjects.
* Seriousness was not collected in STI571BFI03.
95% CI is derived from the Clopper-Pearson formula.
MedDRA version 23.1
Source: [EU RMP version 13.0 Annex 7 - Table 16.4-6.1]

Table 8-4 Important potential risk of tolerability during pregnancy and pregnancy outcomes: other details

Tolerability during pregnancy and pregnancy outcomes	Details
Potential mechanisms	Imatinib was shown to be embryotoxic and teratogenic in rats, but not in rabbits.
Evidence sources and strength of evidence	Information on pregnancy in patients with CML in the pre-imatinib era is scarce. Several case reports have been published. Mubarak et al (2002) and Ali et al (2004) described in total 13 cases, all with normal outcome. No incidence rates are available. Singular reports described outcomes of pregnancy in women with ALL. Molkenboer et al (2005) presented 2 cases: one with missed abortion in 6th week and one with stillborn fetus at 22 week of pregnancy. Among 6 pregnancies in patients with ALL reported by Chelghoum et al (2005), 3 ended with therapeutic abortion and 3 with premature birth. In the general population, according to the CDC (2008), the overall prevalence of major defects was 3.0 per 100 in 2005 in the Metropolitan Atlanta Congenital Defects Program (MACDP). This program monitors the prevalence of all major structural or genetic defects at the time of delivery among live births, stillbirths, and pregnancies electively terminated after prenatal diagnosis of defects at >20 weeks' gestation in the five central counties of metropolitan Atlanta. MACDP defines major structural or genetic birth defects as conditions that 1) result from a malformation, deformation, or disruption in one or more parts of the body, a chromosomal abnormality, or a known clinical syndrome; 2) are present at birth; and 3) have a serious, adverse effect on health, development, or functional ability.

Tolerability during pregnancy and pregnancy outcomes	Details
	EUROCAT is a European network of population-based registries for the epidemiologic surveillance of congenital anomalies that was started in 1979 and has surveyed more than 1.7 million births surveyed per year in Europe. It includes data from 43 registries in 23 countries and covers 29% of the European birth population. EUROCAT reported that the prevalence of all anomalies was 2.56 (95% CI: 2.55-2.58) per 100 births (live births (LB), fetal deaths/still births from 20 weeks gestation (FD) and termination of pregnancy for fetal anomaly following prenatal diagnosis (TOPFA)) (EUROCAT 2014). In the general population, spontaneous abortion is the most common complication of early pregnancy, its frequency decreasing with increasing gestational age. Eight to 20 percent of clinically recognized pregnancies at less than 20 weeks of gestation undergo spontaneous abortion with 80% of these occurring in the first 12 weeks of gestation. The overall risk of spontaneous abortion after 15 weeks is low (about 0.6%) for chromosomally and structurally normal fetuses, but varies with the presence of associated risk factors. Loss of unrecognized or subclinical pregnancies occurs in 13 to 26% of all pregnancies. If pre-implantation losses are considered, approximately 50% of fertilized oocytes do not result in a live birth (Tulandi and Al-Fozan 2013).
Characterization of the risk:	The analysis of the cases for the clinical trial data, PSUR reporting interval and cumulative data has not identified a causal association between imatinib and adverse pregnancy outcomes or any new/ changing safety signal pertaining to this potential risk. Fetal outcomes and birth types are consistent with the observations in the general population.
Risk factors and risk groups	Women of childbearing age becoming pregnant and/or requiring treatment with imatinib through pregnancy if treatment cannot be discontinued.
Preventability	Avoiding pregnancy, including highly-effective contraception in women of childbearing age, as advised in the product labeling.
Impact on the benefit-risk balance of the product	Potentially significant as the drug is documented to be embryotoxic and teratogenic in pre-clinical studies. Avoiding pregnancy is recommended.
Public health impact	The possible increased risk to the fetus with continued treatment of CML during pregnancy poses a considerable challenge. Available post-marketing safety reports that have been published might suggest an increased risk of skeletal malformations (Pye et al 2008). Novartis sponsored a non-interventional registration study for pregnancies in patient who have received imatinib or nilotinib: On 26-Feb-2015, the Committee for Medicinal Products for Human Use (CHMP) adopted the conclusions of PRAC and endorsed the termination (MAH request) of the voluntary pregnancy registry due to poor enrollment; and requested the MAH to further strengthen pharmacovigilance data collection for pregnancy outcomes.

8.3.2 SVII.3.2. Presentation of the missing information

Table 8-5 Missing information: Pediatric patients below 2 years of age

Pediatric patients below 2 years of age	Details
Evidence source	There is limited experience with the use of imatinib in pediatric patients <2 years old. Based on pooled population pharmacokinetic analysis in pediatric patients with hematological disorders and physiologically-based PK modeling, exposure of imatinib in pediatric patients aged 1 or above receiving 260 mg/m^2/d (not exceeding 400 mg/d) or 340 mg/m^2/d (not exceeding 600 mg/d) were similar to those in adult patients who received imatinib 400 mg/d or 600 mg/d.

9 Part II Safety specification Module SVIII: Summary of the safety concerns

Table 9-1 Table Part II SVIII.1: Summary of safety concerns

Important identified risks	None
Important potential risks	Second primary malignancy
	Tolerability during pregnancy and pregnancy outcomes
Missing information	Pediatric patients below 2 years of age

10 Part III: Pharmacovigilance plan (including post-authorization safety studies)

10.1 Part III.1. Routine pharmacovigilance activities

10.1.1 Routine pharmacovigilance activities beyond ADRs reporting and signal detection

Specific adverse reaction follow-up checklists

Pregnancy Notification form will be used to collect further data to help further characterize and/or closely monitor the important potential risk of tolerability during pregnancy and pregnancy outcomes.

Other forms of routine pharmacovigilance activities

None

10.2 Part III.2. Additional pharmacovigilance activities

None

10.3 Part III.3 Summary Table of additional pharmacovigilance activities

Table 10-1 Part III.1: Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
None				

11 Part IV: Plans for post-authorization efficacy studies

None.

12 Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)

Risk Minimization Plan

12.1 Part V.1. Routine risk minimization measures

Table 12-1 Table Part V.1: Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Second primary malignancy	**Routine risk communication:** None. However, Section 5.3 of the SmPC provides details about the pre-clinical data on this safety concern. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** None
Tolerability during pregnancy and pregnancy outcomes	**Routine risk communication:** SmPC Section 4.6 SmPC Section 5.3 PL Section 2. **Routine risk minimization activities recommending specific clinical measures to address the risk:** SmPC Section 4.6 and PL Section 2 recommend that imatinib should not be used in pregnancy unless there is a clear necessity. **Other routine risk minimization measures beyond the Product Information:** None
Pediatric patients below 2 years of age	**Routine risk communication:** SmPC Section 4.2 **Routine risk minimization activities recommending specific clinical measures to address the risk:** None. There is no data in this population. **Other routine risk minimization measures beyond the Product Information:** None

12.2 Part V.2. Additional risk minimization measures

Routine risk minimization activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

12.3 Part V.3 Summary of risk minimization measures

Table 12-2 Summary of pharmacovigilance and risk minimization activities by safety concerns

Safety concern	Risk minimization measures	Pharmacovigilance activities
Second primary malignancy	**Routine risk communication** None. However, Section 5.3 of the SmPC provides details about the pre-clinical data on this safety concern. **Additional risk minimization measures:** None	Routine PhV activities beyond adverse reactions reporting and signal detection: None. Additional PhV activities: None
Tolerability during pregnancy and pregnancy outcomes	**Routine risk communication** SmPC Section 4.6 SmPC Section 5.3 PL Section 2. SmPC Section 4.6 and PL Section 2 recommend that imatinib should not be used in pregnancy unless there is a clear necessity. **Additional risk minimization measures:** None	Routine PhV activities beyond adverse reactions reporting and signal detection: Pregnancy form. Additional PhV activities: None
Pediatric patients below 2 years of age	**Routine risk communication** SmPC Section 4.2. There is no data in this population. **Additional risk minimization measures:** None	Routine PhV activities beyond adverse reactions reporting and signal detection: None Additional PhV activities: None

13 Part VI: Summary of the risk management plan for Glivec/ Imatinib

This is a summary of the risk management plan (RMP) for Glivec/ Imatinib. The RMP details important risks of Glivec/ Imatinib, how these risks can be minimized, and how more information will be obtained about Glivec/ Imatinib's risks and uncertainties (missing information).

Glivec and Imatinib's summaries of product characteristics (SmPC) and their package leaflets give essential information to healthcare professionals and patients on how Imatinib should be used.

This summary of the RMP for Glivec and Imatinib should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the Glivec European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Imatinib's RMP.

13.1 Part VI: I. The medicine and what it is used for

Glivec/ Imatinib are authorised for Chronic Myeloid Leukemia (CML), Acute Lymphoblastic Leukemia (ALL) and Gastrointestinal Stromal Tumors (GIST) (see SmPC for the full indication). It contains imatinib as the active substance and it is given by oral route of administration.

Further information about the evaluation of imatinib's benefits can be found in imatinib's European public assessment reports (EPAR), including in its plain-language summary, available on the EMA website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/glivec.

13.2 Part VI: II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of imatinib, together with measures to minimize such risks and the proposed studies for learning more about imatinib's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

13.2.1 Part VI – II.A: List of important risks and missing information

Important risks of imatinib are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of imatinib. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine);

Table 13-1 List of important risks and missing information

List of important risks and missing information	
Important identified risk	None
Important potential risks	Second primary malignancy
	Tolerability during pregnancy and pregnancy outcomes
Missing information	Pediatric patients below 2 years of age

13.2.2 Part VI - II B: Summary of important risks

There are no important identified risks for imatinib.

Table 13-2 Important potential risk: Second primary malignancy

Evidence for linking the risk to the medicine	The severity and nature of an identified malignancy will generally vary with the specific type of malignancy and the promptness with which it is identified and treated. No characteristic pattern has been identified with imatinib. Rebora et al (2010) used the Swedish Cancer Registry to assess the incidence rates of second primary cancers among CML patients. With a total of a 145 subsequent primary malignancies identified in 2,753 adult patients diagnosed with CML between 1970 and 1995, an increased incidence rate of second malignancy was found for all-site cancers (standardized incidence rate – SIR of 1.82, 95%CI: 1.53 – 2.14), stomach cancer (SIR = 2.76, 95%CI: 1.33 – 5.08), skin cancer (SIR = 5.36, 95%CI: 3.18 – 8.47), urogenital tract cancer (SIR = 1.61, 95%CI: 1.15 – 2.21), and lymphoid leukemia (SIR = 5.53, 95%CI: 1.79 – 12.89). Among 856 survivors of childhood ALL, 44 developed second primary neoplasms; 41 of them radiation-related. The risk of a second neoplasm was significantly higher in the 597 patients who received radiation therapy (irradiated group) than in the 259 patients who did not (p=0.04; estimated cumulative risk [+/-SE] at 20 years, 20.9+/-3.9% vs. 0.95+/-0.9%) (Pui et al 2003).
Risk factors and risk groups	Unknown

Risk minimization measures	**Routine risk minimization measures** None. However, Section 5.3 of the SmPC provides details about the pre-clinical data on this safety concern. **Additional risk minimization measures** None

Table 13-3 Important potential risk: Tolerability during pregnancy and pregnancy outcomes

Evidence for linking the risk to the medicine	Information on pregnancy in patients with CML in the pre-imatinib era is scarce. Several case reports have been published. Mubarak et al (2002) and Ali et al (2004) described in total 13 cases, all with normal outcome. No incidence rates are available. Singular reports described outcomes of pregnancy in women with ALL. Molkenboer et al (2005) presented 2 cases: one with missed abortion in 6th week and one with stillborn fetus at 22 week of pregnancy. Among 6 pregnancies in patients with ALL reported by Chelghoum et al (2005), 3 ended with therapeutic abortion and 3 with premature birth. In the general population, according to the CDC (2008), the overall prevalence of major defects was 3.0 per 100 in 2005 in the Metropolitan Atlanta Congenital Defects Program (MACDP). This program monitors the prevalence of all major structural or genetic defects at the time of delivery among live births, stillbirths, and pregnancies electively terminated after prenatal diagnosis of defects at >20 weeks' gestation in the five central counties of metropolitan Atlanta. MACDP defines major structural or genetic birth defects as conditions that 1) result from a malformation, deformation, or disruption in one or more parts of the body, a chromosomal abnormality, or a known clinical syndrome; 2) are present at birth; and 3) have a serious, adverse effect on health, development, or functional ability. EUROCAT is a European network of population-based registries for the epidemiologic surveillance of congenital anomalies that was started in 1979 and has surveyed more than 1.7 million births surveyed per year in Europe. It includes data from 43 registries in 23 countries and covers 29% of the European birth population. EUROCAT reported that the prevalence of all anomalies was 2.56 (95% CI: 2.55-2.58) per 100 births (live births (LB), fetal deaths/still births from 20 weeks gestation (FD) and termination of pregnancy for fetal anomaly following prenatal diagnosis (TOPFA)) (EUROCAT 2014). In the general population, spontaneous abortion is the most common complication of early pregnancy, its frequency decreasing with increasing gestational age. Eight to 20 percent of clinically recognized pregnancies at less than 20 weeks of gestation undergo spontaneous abortion with 80% of these occurring in the first 12 weeks of gestation. The overall risk of spontaneous abortion after 15 weeks is low (about 0.6%) for chromosomally and structurally normal fetuses, but varies with the presence of associated risk factors. Loss of unrecognized or subclinical pregnancies occurs in 13 to 26% of all pregnancies.

	If pre-implantation losses are considered, approximately 50% of fertilized oocytes do not result in a live birth (Tulandi and Al-Fozan 2013).
Risk factors and risk groups	Women of childbearing age becoming pregnant and/or requiring treatment with imatinib through pregnancy if treatment cannot be discontinued
Risk minimization measures	**Routine risk minimization measures** SmPC Section 4.6 SmPC Section 5.3 PL Section 2. SmPC Section 4.6 and PL Section 2 recommend that imatinib should not be used in pregnancy unless there is a clear necessity. **Additional risk minimization measures** None

Table 13-4 Missing information: Pediatric patients below 2 years of age

Risk minimization measures	**Routine risk minimization measures** SmPC Section 4.2. There is no data in this population. **Additional risk minimization measures** None

13.2.3 Part VI – II C: Post-authorization development plan

13.2.3.1 II.C.1 Studies which are conditions of the marketing authorization

None

13.2.3.2 II.C.2. Other studies in post-authorization development plan

None

14 Part VII: Annexes

Annex 4 - Specific adverse drug reaction follow-up forms

Important potential risk: Tolerability during pregnancy and pregnancy outcomes

Pregnancy Notification form (version 1.1)

Gleevec/Glivec Pregnancy Notification Form
Version 1.1

Case ID: _____ Subject Initials: _____ Study Title: _____
Subject ID: _____ Trial Number: _____ Center ID: _____

PATIENT WHO TOOK Gleevec/Glivec (imatinib): FATHER ☐ MOTHER ☐

1. MATERNAL INFORMATION

Date of Birth | Date of last menstrual period | Expected Date of Delivery

Method of contraception: _____

Contraception used as instructed?
Yes ☐ No ☐ Uncertain ☐

2. MEDICAL HISTORY (include information on familial disorders, known risk factors or conditions that may affect the outcome of the pregnancy. If none, mark as N/A)

3. PREVIOUS OBSTETRIC HISTORY (provide details on all previous pregnancies, including termination or stillbirth)

	Gestation Week	Outcome including any abnormalities
1		
2		
3		

4		
5		

4. DRUG INFORMATION (list all therapies taken prior to and during pregnancy)

Name of drug	Daily Dose	Date Started	Date Stopped	Indication	Treatment Start (week of pregnancy)	Treatment Stop (week of pregnancy)

5. PRENATAL INFORMATION

Have any specific tests, e.g. amniocentesis, ultrasound, maternal serum AFP, been performed during the pregnancy so far?Yes☐ No☐ Not Known☐

If Yes, please specify test date and results:

Test _____ Date ____

Result _____

6. PREGNANCY OUTCOME

(a) Abortion: Yes☐ No☐

If Yes,

Therapeutic☐ Planned☐ Spontaneous ☐

(b) Delivery:Yes☐No☐

If Yes,

Normal☐ Caesarean☐ Forceps/Ventouse☐

Please specify the reason and any abnormalities (if known):

_____

_____

_____

Maternal complications or problems related to birth:

_____

_____

_____

Date of Abortion: ____

Delivery at week: ____

7. MATERNAL PREGNANCY ASSOCIATED EVENTS

If the mother experiences an SAE during the pregnancy, please indicate here and complete an SAE form and submit immediately

8. CHILD OUTCOME

Normal☐ Abnormal☐ Stillbirth☐

If any abnormalities, please specify and provide dates

Sex:Male☐ Female☐

Height ⌊_⌋ cm

Weight ⌊_⌋ kg

Head circumference ⌊_⌋ cm

Apgar Scores:

1 min ⌊_⌋

5 min ⌊_⌋

10 mins ⌊_⌋

9. ASSESSMENT OF SERIOUSNESS (OF PREGNANCY OUTCOME)

Non serious ☐

Involved prolonged inpatient hospitalization ☐

Results in persistent or significant disability/incapacity ☐

Life-threatening ☐

Mother died ☐

Date of death ⌊_⌋

Stillbirth/neonate died ☐

Date of death ⌊_⌋

Other Seriousness criteria

Congenital anomaly/birth defect ☐

Other Significant medical events ☐

10. ASSESSMENT OF CAUSALITY (OF PREGNANCY OUTCOME)

Please indicate the relationship between pregnancy outcome

Unrelated ☐ Possibly* ☐ Probably* ☐ Definitely* ☐

If any of the fields marked * have been checked, the outcome is considered to be RELATED to the study drug.

11. ADDITIONAL INFORMATION

12. INFORMATION SOURCE

HCP Details:

Name _____

Address

_____

Date of report |_|_|_|_|_|_|_|_|

HCP Signature _____

Annex 6 - Details of proposed additional risk minimization activities (if applicable)

Not applicable.