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.

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.

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.

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 0-1 List of important risks and missing information

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

II B: Summary of important risks

There are no important identified risks for imatinib.

Table 0-2 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 0-3 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 0-4 Missing information: Pediatric patients: long term follow up

Risk minimization measures	**Routine risk minimization measures** SmPC Section 4.4 SmPC Section 4.9 PL Section 2 **Additional risk minimization measures** None
Additional Pharmacovigilance Activities	**Additional pharmacovigilance activities:** Study CSTI571I2201 See section II.C of this summary for an overview of the post-authorization development plan.

Table 0-5 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

II C: Post-authorization development plan

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

Table 0-6 Studies which are conditions of the marketing authorization

Study short name	Purpose of the study:
CSTI571I2201	To collect data on efficacy and safety in pediatric population with newly diagnosed Ph+ ALL patients treated with chemotherapy + imatinib hematopoietic stem cell treatment HSCT).

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

None