5.2 Part VI.2 Elements for a Public Summary

5.2.1 Part VI.2.1 Overview of disease epidemiology

Chronic Myeloid Leukemia (CML)

CML is the most common of the blood cancers. It accounts for 15-20% of all cases of leukemia. Approximately 1-2 people per 100,000 people every year
have CML. People are generally between 45-67 years of age when they are diagnosed. There are slightly more men than women who are diagnosed with CML, and it is slightly more common in Whites and Blacks than in other races (such as Hispanics or Asians).

Ph+ ALL

There are 2 general age groups where people may be diagnosed with Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL).
Group 1: 2-4 years of age
Group 2: more than 50 years of age.
For group 1, 4-5 of every 100 children are diagnosed with Ph+ ALL. For group 2, approximately 1 in every 100,000 people are diagnosed with Ph+ ALL. ALL makes up 75% of all leukemias in children below 15 years of age and 12% in adults.
The number of boys or girls who have Ph+ ALL is about the same. In adults, more men than women have ALL.
Cancer Research UK lists the following risk factors for ALL:

- radiation exposure (such as x-rays)
- exposure to benzene (a chemical found in gasoline and sometimes used in lab
- experiments)
- smoking and coffee drinking
- genetic conditions (such as Down's syndrome)
- past chemotherapy (drugs to treat cancers)
- being overweight
- contact with paint
- having a weak immune system

Gastrointestinal Stromal Tumor (GIST)

Little information is known on how many people have GIST. One study reported 129 for every one million inhabitants in Sweden with GIST. The number of people who have GIST increases with age. GIST may occur in patients with a family history for GIST or some other genetic conditions.

5.2.2 Part VI.2.2 Summary of treatment benefits

Imanitib fight cancer by turning off an enzyme that causes cells to become cancerous and multiply**.** One advantage of Imanitib is that it can be given by mouth instead of by injection. A second advantage is that CML seems to respond relatively quickly (within one to three months) to the drug. This response can be measured by tests that show that the blood count returns to a normal range or tests that measure cancer cells in the bone marrow.[1]

5.2.3 Part VI.2.3 Unknowns relating to treatment benefits

There are no adequate data on the use of imatinib in:

• Children less than 2 years old.

• People with liver problems.

• People with kidney problems.

• Pregnant and breast-feeding women.

5.2.4 Part VI.2.4 Summary of safety concerns

Table 5-5 Important identified risks

Risk	What is known	Preventability
Decrease in the number of cells that help fight infection (white blood cells), carry oxygen (red blood cells), and help with normal blood clotting (platelets) (Myelosuppression) CML	CML: Some patients with CML who took imatinib had myelosuppression. Most times, the myelosuppression would return to the number of cells the patient had before taking imatinib when imatinib was stopped for a short period of time or when the dose of imatinib was lowered. A few patients stopped taking imatinib because of myelosuppression. CML and GIST: More patients with CML had a low number of red blood cells and low number of platelets than patients with GIST. Pediatric Ph+ ALL: Some pediatric Ph+ ALL patients who took imatinib had myelosuppression. Most times, the myelosuppression would return to the number of cells the patient had before taking imatinib when imatinib was stopped for a short period of time or when the dose of imatinib was lowered. A few patients stopped taking imatinib because of myelosuppression.	Yes, by regularly having blood tests.
Body holds on to water (Edema and Fluid Retention)	Occurrences of severe fluid retention have been reported in approximately 2.5% of newly diagnosed CML patients taking imatinib.	Yes, by: 1). Using imatinib with extra care in patients with heart problems, 2). Increasing the dose of imatinib slowly in elderly patients 3). Increasing the dose of imatinib slowly in patients with other problems that might cause them to hold onto water, 4). Monitoring patients for swelling or weight gain and giving diuretics (“water pill”) if needed.
Bleeding in the brain and in digestive organs (such as	Patients with GIST that cannot be treated with surgery or where the	Yes, by regularly having blood tests (Complete Blood Count),

Risk	What is known	Preventability
stomach and intestines) (CNS and GI Hemorrhages)	cancer has spread to other parts of the body had gastrointestinal hemorrhages and hemorrhages within the tumor. There are currently no predisposing causes (such as the size or the location of the tumor size) have been identified that place patients with GIST at a higher risk of either CNS or GI hemorrhage. An increased number of blood vessels and a tendency for a greater amount of bleeding is a part of the nature GIST. All patients should be monitored for a hemorrhage. Pediatric Ph+ ALL: Hemorrhage does not appear to be an important risk for pediatric patients with Ph+ ALL.	and in particular, the number of thrombocytes (platelets).
A blockage, tear, or break in one of the digestive organs (such as the stomach or intestines) (Gastrointestinal Obstruction, Perforation, or Ulceration)	Cases of gastrointestinal obstruction, perforation or ulceration have been observed with imatinib.	Preventability is unknown.
Liver damage (Hepatotoxicity)	Cases of liver injury have been observed with imatinib.	Yes, by screening for potential problems like alcohol use and the use of other medications, and laboratory monitoring of liver function.
Skin Rashes and Severe Cutaneous Adverse Reactions (SCARs)	Cases of skin rashes and severe cutaneous adverse reactions have been observed with imatinib.	Preventability is unknown.
Low amount of thyroid hormone in the blood (Hypothyroidism)	Clinical cases of hypothyroidism have been reported in thyroidectomy patients undergoing levothyroxine replacement during treatment with imatinib.	Thyroid-stimulating hormone (TSH) levels should be closely monitored in such patients.
Low amount of phosphorous in the blood (Hypophosphatemia)	Cases of hypophosphatemia have been observed with imatinib.	Yes, by testing the amount of phosphate in the blood.
Heart is weak and not able to pump blood well (Cardiac Failure)	Cardiac adverse events have been reported uncommonly with imatinib.	Yes, by screening the patient before taking imatinib and monitoring the patient while taking imatinib for any signs or symptoms of heart failure such as fluid retention.

Risk	What is known	Preventability
Rapid loss of the ability of the kidney to remove waste and help balance fluids (Acute Renal Failure)	Cases of acute renal failure have been observed with imatinib.	Yes, by regularly testing serum creatinine in the blood.
Severe breathing-type problems(Severe Respiratory Adverse Reactions)	Cases of acute renal failure have been observed with imatinib.	Yes, by physical examination and lung function tests.
Muscle tissue break down and muscle weakness due to muscle fibers not functioning well (Rhabdomyolysis and Myopathy)	Cases of rhabdomyolysis and myopathy have been observed with imatinib.	Yes, by monitoring for signs and symptoms of rhabdomyolysis (such as muscle pain and dark urine) and the use of other medications
Bleeding from the ovary and bleeding from a cyst on the ovary (in females) (Ovarian Hemorrhage and Hemorrhagic Ovarian Cyst)	Cases of ovarian hemorrhage and Hemorrhagic ovarian cyst have been observed with imatinib.	Preventability is unknown.
A group of complications caused by the breakdown products of dying cancer cells (such as high amounts of potassium, phosphorous, calcium) that can result in acute renal failure (Tumor lysis syndrome)	Cases of tumor lysis syndrome have been observed with imatinib.	Yes, by drinking plenty of water to maintain high urine output and taking allopurinol to stop uric acid production.
Growth retardation in children	There have been case reports of growth retardation occurring in children and pre-adolescents receiving imatinib. The long-term effects of prolonged treatment with imatinib on growth in children are unknown.	Close monitoring of growth in children under imatinib treatment is recommended
Renal (kidney) impairment associated with long term use	Long-term treatment with imatinib may impair kidney function.	Yes, by regularly testing serum creatinine in the blood.
Interactions with medicines that decrease the function of a liver enzyme called CYP3A4 (Interactions with strong CYP3A4 inhibitors)	Some medicines can interfere with the effect of imatinib when taken together. They may increase or decrease the effect of imatinib, either leading to increased side effects or making imatinib less effective. Imatinib may do the same to some other medicines.	Patients should tell their doctor or pharmacist if they are taking, have recently taken or might take any other medicines.
Interactions with medicines that promote the function of a liver enzyme called	Some medicines can interfere with the effect of imatinib when taken together. They may increase or	Patients should tell their doctor or pharmacist if they are taking, have recently taken or might

Risk	What is known	Preventability
CYP3A4 (Interactions with strong CYP3A4 inducers)	decrease the effect of imatinib, either leading to increased side effects or making imatinib less effective. Imatinib may do the same to some other medicines.	take any other medicines.
Interactions with medicines that are removed from the body by a liver enzyme called CYP3A4 (Interactions with drugs eliminated by CYP3A4)	Some medicines can interfere with the effect of imatinib when taken together. They may increase or decrease the effect of imatinib, either leading to increased side effects or making imatinib less effective. Imatinib may do the same to some other medicines.	Patients should tell their doctor or pharmacist if they are taking, have recently taken or might take any other medicines.

Table 5-6 Important potential risks

Risk	What is known
A new cancer that happens in the background of the first cancer (example: skin cancer that is found after being treated for leukemia) (Second Malignancies in Survivors)	A review of available information did not provide proof for an increase in the number of new cancers in people who took imatinib.
Small blood clots form inside the blood vessels throughout the body (Disseminated Intravascular Coagulation)	There are insufficient data on disseminated intravascular coagulation.
Low blood sugar (Hypoglycemia)	There are insufficient data data on hypoglycemia.
Likelihood of someone thinking about or trying to kill oneself (Suicidality)	There are insufficient data data on suicidality.
Tolerability during Pregnancy and Pregnancy Outcome	Imatinib should be avoided during pregnancy. An unborn baby coming in contact with imatinib through the mother during pregnancy might result in an increased chance of the baby having problems, being deformed, or the baby dying before birth. Women of childbearing potential should use birth control while taking imatinib.
Interactions with medicines that are removed from the body by liver enzymes called CYP2C9, CYP2C19 and CYP2D6 (Interactions with drugs eliminated by CYP2C9, CYP2C19 and CYP2D6)	Some medicines can interfere with the effect of imatinib when taken together. They may increase or decrease the effect of imatinib, either leading to increased side effects or making imatinib less effective. Imatinib may do the same to some other medicines. Patients should tell their doctor or pharmacist if they are taking, have recently taken or might take any other medicines.
Interactions with acetaminophen/ paracetamol	Some medicines can interfere with the effect of imatinib when taken together. They may increase or decrease the effect of imatinib, either leading to increased side effects or making imatinib less effective. Imatinib may do the same to some other medicines. Patients should tell their doctor or pharmacist if they are taking, have recently taken or might take any other medicines.

Table 5-7 Missing information

Risk	What is known
Pediatric Patients: Long term Follow up	Children have been given imatinib and had check-ups for a long time after they took imatinib. The potential effect of imatinib on a child's growth and developmentis currently being addressed in a pediatric registry.
Pediatric patients below 2 years of age	There are insufficient data on the use of imatinib in children below 2 years of age.
Renal impairment	Patients with mild or moderate kidney problems should be given the minimum recommended dose of 400 mg daily as starting dose. This is because only a small amount of Imatinib is removed from the body. Only a very small amount of information is available in patients with severe kidney problems who are on dialysis (where a machine 'cleans' the blood like the kidneys would do). If you are on dialysis you are able to start at a dose of 400 mg per day, but with caution. Your physician can adapt your dose if necessary.
Hepatic impairment	Imatinib is broken down in the body mainly by the liver. Patients with GIST might have cancer that has spread to the liver and, therefore, may have liver problems. Patients with mild, moderate or severe liver problems should be given the minimum recommended dose of 400 mg daily. Your physician can adapt your dose if necessary.
Elderly patients	No age-related significant difference in safety and efficacy has been observed in clinical studies. Imatinib has been effectively and safely administered as induction therapy in elderly (age ≥ 55 years) Ph+ ALL patients as a single-agent.

5.2.5 Part VI.2.5 Summary of additional risk minimization measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

5.2.6 Part VI.2.6 Planned post authorization development plan

None

5.2.7 Part VI.2.7 Summary of changes to the Risk Management Plan over time

Not applicable (first submission)