Imatinib Fresenius Kabi 100 mg and 400 mg film-coated tablets

30.6.2015, Version 1.1

PUBLIC SUMMARY OF THE RISK MANAGEMENT PLAN

VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Chronic myeloid leukaemia (CML)

Chronic myeloid leukaemia (CML), a cancer of the white blood cells in which granulocytes (a type of white blood cell) start growing out of control. Imatinib is used when the patients are 'Philadelphia chromosome positive' (Ph+). This means that some of their genes have re-arranged themselves to form a special chromosome called the Philadelphia chromosome. There is a slight male preponderance (male-to-female ratio 1.6:1). Incidence remains almost constant all over the world. Its annual incidence is about 1.5 cases per 100,000 individuals. This incidence has not changed over in the past few decades and it increases with age. The median age at diagnosis is 55-60 years; it is uncommon in children and adolescents; only 2.7% of CML cases are younger than 20 years. [1]

Ph+ acute lymphoblastic leukaemia (ALL)

Ph+ acute lymphoblastic leukaemia (ALL), a type of cancer in which lymphocytes (another type of white blood cell) multiply too quickly. ALL is the most common cancer in childhood (0-14 years) constituting slightly less than one-third of all childhood cancers diagnosed, while in adolescents and young adults (15-19 years) it constitutes approximately 10% of cancers diagnosed. It was found that 5-year survival for ALL in European children and young adults improved significantly from 1995 and 2002, although survival was poorer in adolescents and young adults than children.[2]

For ALL, incidence was high at 0-14 years (3.59; 3.40-4.78), decreased to 0.53 (0.45-0.61) at 45-54 years and increased with advancing age thereafter (to 1.45; 1.27-1.65, at 75-99 years).[3]

Myelodysplastic or Myeloproliferative Diseases (MD/MPD)

Myelodysplastic or myeloproliferative diseases, a group of diseases in which the body produces large numbers of abnormal blood cells. Incidence rates increased with age and were higher among males than females. The incidence rate of Myelodysplastic or Myeloproliferative Diseases estimated for the United States in 2001 through 2003 (3.3 per 100,000) is remarkably similar to those previously reported from European countries, including England and Wales (3.6 per 100,000), Germany (4.1 per 100,000), Sweden (3.6 per 100,000) and France (3.2 per 100,000).[4]

Hypereosinophilic Syndrome (HES)

Advanced hypereosinophilic syndrome or chronic eosinophilic leukaemia (CEL), diseases in which eosinophils (another type of white blood cell) start growing out of control. The age of onset of HES is variable, occurring anywhere from early childhood to extreme old age, although the majority (70%) of patients have onset between 20 and 50 years of age. The majority of patients (approximately three-

quarters) described in reports from Europe and North America were Caucasian, and males were more likely to be afflicted than females, with male/female ratios ranging from 4:1 to 9:1.[5]

Dermatofibrosarcoma Protuberans (DFSP)

Dermatofibrosarcoma protuberans, a type of cancer (sarcoma) in which cells in the tissue beneath the skin divide uncontrollably. DFSP is one of the rarest skin cancers (less than 1 case per 100,000 people annually). However, it is the most common cutaneous sarcoma. The tumor generally presents in middle age, with an average age of onset at 40 years. Tumors presenting at birth or in childhood have, however, been reported. Males and females are equally affected; the mortality rate accompanying low metastatic rate is very low.[8]

VI.2.2 SUMMARY OF TREATMENT BENEFITS

For CML, Imatinib has been examined in a reported study involving 1,106 adults that compared Imatinib with the combination of interferon alpha plus cytarabine (other anticancer medicines). This study measured how long the patients lived without their cancer getting worse.

For Ph+ ALL, Imatinib has been examined in three reported studies involving 456 adults, including one study comparing Imatinib with standard chemotherapy (medicines used to kill cancer cells) in 55 newly diagnosed patients. It has also been examined in a fourth main study involving 160 children and young people aged 1 to 22 years.

For MD/MPD (31 patients), HES and CEL (176 patients), and DFSP (18 patients), these studies examined whether blood cell counts returned to normal levels, or whether the number of cancerous blood cells or the size of tumours fell.

Imatinib was more effective than the comparator medicines. In patients with CML, the cancer had got worse in 16% of the patients taking Imatinib after five years, compared with 28% of those taking interferon alpha plus cytarabine. Imatinib was also better than standard chemotherapy in patients with Ph+ ALL. In the non-comparative studies of CML and Ph+ ALL, between 26 and 96% of patients showed a response to Imatinib. In the study of patients aged 1 to 22 years who had Ph+ ALL, Imatinib was shown to increase how long the patients lived without any major events (such as a relapse).

VI.2.3 UNKNOWNS RELATING TO TREATMENT BENEFITS

Different people respond differently to medication depending on which ethnic group they belong, their age or genetic background.

There is no experience in children with CML below 2 years of age and with Ph+ALL below 1 year of age.

Use of Imatinib with elderly patients has not been studied so there is limited data available regarding the use of imatinib in eldery patients age group.

Studies on patients receiving imatinib and its effect on fertility and gametogenesis have not been performed so there is limited data available regarding the affect of imatinib on the fertility of the patients.

VI.2.4 SUMMARY OF SAFETY CONCERNS

Safety Concern	What is known	Preventability
Important Identified Risks		
Reduction in the number of white blood cells (Neutropenia), Reduction in blood platelets (Thrombocytopenia) (Myelosuppression)	Reduction in the number of white blood (symptoms included frequent infections such as fever, severe chills, sore throat or mouth ulcers) and blood platelets (symptoms included bleeding or bruising more easily than normal) have been reported with the use of imatinib therapy.	Yes by monitoring of early symptoms. You should inform your doctor immediately if you feel tiredness, headache, chill, fever, bleeding or any infection. Routine monitoring of blood cell counts is recommended. Your doctor may reduce the dose of imatinib if your blood cell count is low. Do not take imatinib if you suffer from severe suppression of bone marrow functionality, symptoms may be: extreme tiredness, easy bruising or bleeding, occurrence of infections.
Swelling (oedema) and Fluid retention	Occurrences of severe fluid retention [accumulation of fluid in the chest or on the lung (pleural effusion), swelling (oedema), fluid in the lung (pulmonary oedema), swelling due to build-up of fluid around the stomach (ascites)] have been reported in some newly diagnosed Chronic myeloid leukaemia [a cancer of the white blood cells in which granulocytes (a type of white blood cell) start growing out of control] patients taking imatinib. In clinical trials, more cases of these events reported in older people and those with a prior history of heart disease.	Yes by monitoring of early symptoms. Tell your doctor immediately if you notice any weight gain, breathing problem or generalized swelling. If you have any prior history of heart disease, inform your doctor before starting imatinib therapy.
Bleeding from the brain and stomach or intestinal wall (CNS and GI haemorrhage)	Cases of bleeding from the brain and stomach and/or intestinal wall have been reported with the use of	Yes can be prevented by the detection of early stage symptoms.

Safety Concern	What is known	Preventability
	imatinib therapy in the patients with Gastrointestinal stromal tumours, a type of cancer (sarcoma) of the stomach and bowel.	Stop taking imatinib and inform your doctor immediately if you have notice any kind of bleeding symptoms like vomiting blood or material that looks like coffee grounds, bleeding from the back passage, black sticky bowel motions (stools) or bloody diarrhoea.
Gastrointestinal Obstruction, Perforation, or Ulceration	Cases of gastrointestinal obstruction, perforation, or ulceration have been reported with the use of imatinib therapy.	Yes with the monitoring of early detection symptoms. Stop taking imatinib and inform your doctor immediately if you have notice any kind of bleeding from the back passage, black sticky bowel motions (stools), heaviness in stomach, stomach pain.
Liver disorder (Hepatotoxicity)	Cases of liver injury, including liver failure and liver tissues death (hepatic necrosis), have been observed with imatinib. When imatinib is combined with high dose chemotherapy regimens, an increase in serious liver reactions has been detected.	Yes by detection of early monitoring of symptoms. Tell your doctor immediately if you notice any type tiredness, loss of appetite, feeling sick (nausea), sleepiness, and diarrhea. Routine test of your liver function is recommended while you are taking imatinib therapy.
Skin Rashes and Severe Cutaneous Reactions	Clinical cases of Skin Rashes and Severe Cutaneous Reactions have been reported in thyroidectomy (removal of the thyroid gland) patients undergoing levothyroxine replacement during treatment with imatinib	Yes with the monitoring of early detection symptoms. Tell your doctor immediately if you have notice any redness, pain, red skin rash, hives, itchy swelling on skin, pigmentation etc. Do not take imatinib medicine if you have any of these symptoms.

Safety Concern	What is known	Preventability
An underactive thyroid gland (Hypothyroidism)	Clinical cases of An underactive thyroid gland causing a decrease in metabolism have been reported in thyroidectomy (removal of the thyroid gland) patients undergoing levothyroxine replacement during treatment with imatinib	Yes with the monitoring of early detection symptoms. If you notice tiredness, lethargy, muscle weakness, cramps, feeling the cold, a slow heart rate, dry and flaky skin, hair loss, a deep and husky voice, weight gain tell your doctor immediately.
Low phosphate levels in the blood (Hypophosphataemia)	Clinical cases of low phosphate levels in the blood have been reported during treatment with imatinib.	Yes with the monitoring of early detection symptoms. Tell your doctor immediately if you have feel any muscle weekness, tiredness etc. Your doctor may need to perform some lab test to monitor your blood phosphate level during the imatinib therapy.
Heart failure	Heart failure means that the heart muscle cannot pump blood strongly enough to supply all the blood needed throughout the body. Heart failure is not the same as heart attack and does not mean that the heart stops. Heart failure may start off with no symptoms, but as the condition progresses, patients may feel short of breath or may get tired easily after light physical activity such as walking. Some patients may wake up short of breath at night. Fluid may collect in different parts of the body, often first noticed as swollen ankles and feet. Cases of heart failure or dysfunction and cardiac adverse events have been reported in the patients of hypereosinophilic syndrome/ Myelodysplastic or	Yes can be prevented by the detection of early stage symptoms. Tell your doctor immediately if you have notice symptoms like difficulty in breathing, shortness of breathing, exertion, may get tired easily after light physical activity such as walking etc. If you have any prior history of heart disease of kidney disease, inform your doctor before starting imatinib therapy. Routine monitoring of heart function test is recommended.

Safety Concern	What is known	Preventability
	myeloproliferative diseases with the use of imatinib therapy.	
Kidney Failure (kidney disease where you pass little or no urine)	Some cases of kidney disease where you pass little or no urine have been reported during the imatinb therapy. Kidney function should, therefore, be evaluated prior to the start of imatinib therapy and closely monitored during therapy, with particular attention to those patients exhibiting risk factors for renal dysfunction. If kidney dysfunction is observed, appropriate management and treatment should be prescribed in accordance with standard treatment guidelines.	Yes can be prevented by the detection of early stage symptoms. If you have notice any symptoms like little or no urine, drowsiness, nausea, vomiting, breathlessness nausea, loss of appetite, weakness etc inform you doctor immediately. Routine monitoring of kidney function test is recommended.
Breathing problems (Severe Respiratory Adverse Reaction)	Cases of breathing related problems have been reported during the imatinb therapy.	Yes can be prevented by the detection of early stage symptoms. If you have notice any breathing problems, difficulty in breathing, swallowing, swelling in chest region, cough etc inform you doctor immediately.
Temporary paralysis or weakness of muscles (Rhabdomyolysis) and disease of muscle (Myopathy)	Cases of Temporary paralysis or weakness of muscles (Rhabdomyolysis) and disease of muscle (Myopathy) have been reported during the imatinb therapy.	Yes can be prevented by detection of any growth retardation. If you have notice any aching muscles, muscle tenderness or weakness, not caused by exercise, dark red or cola coloured urine, general weakness, muscle stiffness, joint pain etc inform you doctor immediately.

Safety Concern	What is known	Preventability
Ovarian bleeding (Haemorrhage) and Haemorrhagic Ovarian Cyst	Rare cases of Ovarian bleeding (Haemorrhage) and Haemorrhagic Ovarian Cyst have been reported during the imatinib therapy.	Tell your doctor immediately if you feel symptoms like Dull aching pain within the abdomen or pelvis, irregular periods, Fullness, heaviness, pressure, swelling, or bloating in the abdomen, sudden and sharp pain in the lower abdomen on one side during the imatinib therapy. Do not take imatinib if you notice above symptoms. You doctor may perform ultrasound of your pelvis region.
Tumor lysis syndrome	Tumor lysis syndrome is the term applied to the rapid death of cancer cells and releases their contents to blood stream that exceeds the body's ability to deal with the consequences like increase level of uric acid (hyperuricemia), increase level of potassium ions (hyperkalemia), increase level of phosphate ions (hyperphosphatemia), and decrease level of calcium ions (hypocalcemia). Rare cases of Tumor lysis syndrome has been reported with the use of imatinib therapy.	Yes can be prevented by the detection of early stage symptoms. Tell your doctor immediately if you have noticed any symptoms of urine problems like pain while passing urine, blood in urine, less amout of urine etc, or symptoms of hyperkalemia like weakness, fast or irregular heart beats, paralysis etc. or symptoms of hypocalcemia/ hyperphosphatemia like vomiting, cramps, seizures, spasms, altered mental status numbness or tingling etc. Tell your doctor if you have any prior history of renal disease or heart disease. Close monitoring renal function tests with imatinib treatment is recommended.
Growth retardation in children	There have been case reports of growth retardation occurring in	Yes can be prevented by detection of any growth retardation.

Safety Concern	What is known	Preventability
	children and pre-adolescents receiving imatinib.	Inform your doctor immediately if you noticed any growth retardation in your children with imatinib therapy. Close monitoring of growth in children under imatinib treatment is recommended.
Interaction with strong CYP3A4 inhibitors	Concomitant use of medicines like Protease inhibitors like indinavir, ritonavir (medicines used to treat viral infection), Azole antifungals like ketoconazole, itroconazole (medicines used to treat fungal infection), Certain macrolides like erythromycin, clarithromycin (medicines used to treat bacterial infection) can lead to increase in plasma concentration of imatinib due to inhibit the CYP3A4 enzyme (enzyme which require to metabolize imatinib) activity. High concentration of imatinib can leads to other toxicities so caution should be taken when administering imatinib with inhibitors of the CYP3A4 family that leads to increase concentration of imatinib.	If you are taking another medicine than stop taking them or discontinue the treatment with the imatinib. Before starting therapy with imatinib inform your doctor about any medicine which you have taken in the past or you are taking to treat another disease.
Interaction with strong CYP3A4 inducers	Concomitant use of substances like dexamethasone (medicine use to treat inflammation), phenytoin, carbamazepine, rifampicin, Phenobarbital (medicines used to treat convulsion) and Hypericum perforatum (also known as St. John's Wort) (herb used to treat dipression) may decrease imatinib concentration by inducing the CYP3A4 enzyme (enzyme which require to metabolize imatinib) activity.	If you are taking another medicine than stop taking them or discontinue the treatment with the imatinib. Before starting therapy with imatinib inform your doctor about any medicine which you have taken in the past or you are taking to treat another disease.

Safety Concern	What is known	Preventability
	Decrease in imatinib concentration can potentially increase the risk of therapeutic failure so caution should be taken when administering imatinib with inducer of the CYP3A4 family that leads to decrease concentration of imatinib.	
Interaction with drugs eliminated by CYP3A4	Concomitant use of imatinib with CYP3A4 substrate like Simvastatin (medicine used to treat high cholesterol) may leads to increase in the concentration of simvastatin. Therefore, caution is recommended when administering imatinib with CYP3A4 substrates with a narrow therapeutic window (e.g. cyclosporine, pimozide tacrolimus, sirolimus, ergotamine, diergotamine, fentanyl, alfentanil, terfenadine, bortezomib, docetaxel and quinidine)	If you are taking another medicine than stop taking them or discontinue the treatment with the imatinib. Before starting therapy with imatinib inform your doctor about any medicine which you have taken in the past or you are taking to treat another disease.

Important Potential Risks

Risk	What is known (Including reason why it is considered a potential risk)
Second Malignancy in Survivors	Non clinical data suggest that after the imatinib therapy some animal study cases of second malignancy have been reported. Therapy should be initiated by a physician experienced in the treatment of patients with haematological malignancies and malignant sarcomas, as appropriate.
Disseminated Intravascular Coagulation	Disseminated Intravascular Coagulation is a disorder in which the proteins that control blood clotting become over active. There is a lack of conclusive data indicating causal relationship of Disseminated Intravascular Coagulation with imatinib therapy at this time. Caution should therefore be exercised when using imatinib therapy.
Low blood sugar (Hypoglycaemia)	There is a lack of conclusive data indicating causal relationship of low blood sugar (hypoglycaemia) with imatinib therapy at this time.

	Symptoms of hypoglycaemia are sweating, weakness, hunger, dizziness, trembling, headache, flushing or paleness, numbness, having a fast, pounding heart beat. Caution should therefore be exercised when using imatinib therapy.
Suicidality	There is a lack of conclusive data indicating causal relationship of tendancy to suicide with imatinib therapy at this time. Caution should therefore be exercised when using imatinib therapy.
Tolerability during Pregnancy and Pregnancy Outcome	Imatinib may cause foetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant woman. If the drug is used during pregnancy or if the patient becomes pregnant while receiving this drug, the patient should be informed of the potential hazard to the foetus. If you are pregnant or breast feeding, think you may be pregnant or are planning to have a baby, ask your doctor before you receive treatment with imatinib. Women must not be pregnant during treatment with Imatinib and up to 6 months after treatment. Adequate contraceptive precautions should be used when either partner is receiving Imatinib therapy.
Interaction with dugs eliminated by CYP2C9, CYP2C19 and CYP2D6	Non clinical data suggest that concomitant use of imatinib with metaprolol (medicine to treat uneven heart beat) can increase the concentration of metaprolol. Caution should therefore be exercised when using imatinib and metaprolol concomitantly.
Interaction with acetaminophen/paracetamol (medicine to treat pain and fever)	Non clinical data suggested that imatinib inhibit the paracetamol activity. However higher doses of imatinib and paracetamol have not been studied. Caution should therefore be exercised when using high doses of imatinib and paracetamol concomitantly.
Use in Renal impairment Patients	In patients with impaired renal function, imatinib plasma exposure seems to be higher than that in patients with normal renal function, in these patients. Patients with renal impairment should be given the minimum starting dose. Patients with severe renal impairment should be treated with caution. The dose can be reduced if not tolerated.

Missing Information

Risk	What is known
Pediatric Patient: Long term Follow up	There have been case reports of growth retardation occurring in children and pre-adolescents receiving imatinib. The long-term effects of prolonged treatment with imatinib on growth in children are unknown. Therefore, close monitoring of growth in children under imatinib treatment is recommended.

Pediatric patients below 2 years of age	There is no experience in children with CML below 2 years of age and with Ph+ALL below 1 year of age. Hence cautions should be taken while use imatinib in the pediatric populations below 2 years of age.
Kidney disorder	In patients with impaired kidney function, imatinib plasma exposure seems to be higher than that in patients with normal renal function, probably due to an elevated plasma level of alpha-acid glycoprotein (AGP), an imatinib-binding protein, in these patients. Patients with renal impairment should be given the minimum starting dose. Patients with severe renal impairment should be treated with caution. The dose can be reduced if not tolerated."
Liver disorder	Imatinib is mainly metabolised through the liver. Patients with mild, moderate or severe liver dysfunction should be given the minimum recommended dose of 400 mg daily. The dose can be reduced if not tolerated. Liver function (transaminases, bilirubin, alkaline phosphatase) should be monitored regularly in patients receiving imatinib.
Elderly patients	Safety of imatinib has not been studied in the elderly population. Hence cautions should be taken while use imatinib in the elderly populations.

VI.2.5 SUMMARY OF RISK MINIMISATION MEASURES BY SAFETY CONCERN

The Summary of product characteristics of Imatinib 100 mg film coated tablets and Imatinib 400 mg film coated tablets contain information about routine risk minimisation measures.

VI.2.6 PLANNED POST-AUTHORISATION DEVELOPMENT PLAN

Not applicable.

VI.2.7 SUMMARY OF CHANGES TO THE RISK MANAGEMENT PLAN OVER TIME

Not applicable.