VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

The epidemiology of Philadelphia chromosome (bcr-abl) positive (Ph+) chronic myeloid leukaemia (CML):

CML is a cancer of the white blood cells. It is a form of leukemia (cancer of blood or bone marrow which produces blood cells) in which there is an increased and not controlled growth of myeloid cells [large cells that form granulocytes (white blood cells with presence of granules)] in the bone marrow and the gathering of these cells in the blood.

The occurrence rate of CML ranges between 10 and 15 cases out of 1,000,000 people per year without any major geographic or ethnic differences. The median (the middle most value of data arranged in increasing or decreasing order) age at diagnosis ranges between 60 and 65 years in Europe, but is considerably lower in countries where the population is younger. The number of people with CML is rising due to the increase in survival that has been achieved with cancer curing treatments [1]

Occurrence rates changes from 0.6 to 2.0 cases per 100 000 persons, increase with age and are higher in men than in women. Geographic and/or ethnic changes might contribute to the variability of occurrences among registries. [2]

The epidemiology of Myelodysplastic syndromes (MDS) and myeloproliferative disorders:

Myelodysplastic syndromes (MDS) are different kind of blood cancers with serious problem, occurrence rate and death rate. . It is found that greater than 10,000 new cases of MDS occur in the United States yearly, and that greater than60,000 people with MDS at present stay in the country. With an aging population and an improving awareness of the problem, the problem burden is expected to increase. . Present data suggest that MDS is mainly a problem of the older people. Approximately 86 out of 100 patients with MDS were aged greater than 60 years at the time of their detection, and only 6 out of 100 cases were detected in those aged less than equal to 50 years. Men have a higher occurrence rate than women, and white people have a higher occurrence rate than other racial/ethnic groups.[3]

The occurrence rate of polycythemia vera (PV) and essential thrombocythemia (ET) in a year is approximately 2 and 1.5 per 100,000 people, respectively. [4]

In a study, with an objective to find patterns of survival in 9,384 Myeloproliferative neoplasms (MPN) patients relative survival ratios were taken as measures of patient survival. Relative survival was lower in all MPN subtypes compared to expected survival in the general population, reflected in 10 years relative survival ratios respectively.[5]

The epidemiology of gastrointestinal stromal tumors (GIST):

GIST are the most common tumours (swelling) of the stomach and gut (gastrointestinal tract). Gastrointestinal stromal tumours represents less than 1out of 100 of all digestive tract tumours. The total cases of stromal tumours amounts to 20 to 40 per million people per year. It has been found that total cases of GIST, including both tumours that spread (malignant) and that do not spread (benign) to other body parts, was 15 to 16 per million people per year. According to Polish data, 48 out of 100 GIST patients were women and 52 out of 100 were men, however among the patients with cancer that spread to other parts (metastatic) men outnumber women by far. It was found, that about 20 out of 100 tumours show themselves in patients below 40 years of age and rare during the first 20 years of age. Metastatic disease is more common in younger patients.[6]

The epidemiology of Dermatofibrosarcoma protuberans (DFSP):

Dermatofibrosarcoma protuberans (DFSP) is a rare tumour of the skin, with an occurrence rate of 1 to 5 cases per 1 million people per year. Male patients were affected 1.2 times as often as female patients were. DFSP occurred mainly in young adults between 20 and 39 years of age. [7]. A study of the population-based National Cancer Registry showed the

occurrence rate of DFSP was approximately 4 cases per 100,000 per year in Sweden from 1990-2005. [8]

VI.2.2 Summary of treatment benefits

Philadelphia chromosome (bcr-abl) positive (Ph+) chronic myeloid leukaemia (CML):
In a study, 237 patients with Philadelphia chromosome (Ph)-positive accelerated-phase CML were treated with oral imatinib mesylate at daily doses of 400 mg (26 patients) or 600 mg (211 patients). It was found that imatinib mesylate was effective against Ph-positive, accelerated-phase CML. [9]

Myeloproliferative diseases
In a study, four patients who had long-term myeloproliferative problems and chromosomal translocations (process in which a segment from one chromosome is transferred to other chromosome or to a new site on the same chromosome) were treated with imatinib mesylate (400 mg daily). In all four patients, a normal blood count was achieved within four weeks after treatment began. All responses were long lasting at 9 to 12 months of follow-up. It was concuded that imatinib mesylate produced long lasting responses in patients with long-term myeloproliferative diseases problems associated with activation of platelet-derived growth factor receptor beta (PDGFRB). [10]

Gastrointestinal stromal tumours

In a study aimed to find the anti-tumour response and time to progression (TTP) of patients treated with imatinib mesylate who had (advanced and/or metastatic) tumours that spread GIST or other soft tissue sarcomas (STS). They were treated with imatinib mesylate at the dose of 400 mg twice daily (bid). 73 out of 100 GIST patients were free from progression at 1 year. In the other STS group, there were no objective responses. Imatinib mesylate is well tolerated at a dose of 400 mg bid. This dose was effective in patients with KIT-Ph+ GIST, but patients with other STS subtypes were unlikely to benefit.[11]

Dermatofibrosarcoma protuberans

In a study of imatinib (400 to 800 mg daily) sixteen and eight patients with locally (advanced or metastatic) tumours that spread DFSP were included onto the European Organization for Reasearch and Treatment (EORTC) and Southwest Oncology Group (SWOG) trials, respectively. It was concluded that imatinib was effective in DFSP including fibrosarcomatous DFSP, with objective response rate in nearly 50 out of 100 patients. Response rates and TTP did not differ between patients taking 400 mg daily versus 400 mg twice a day [12]

VI.2.3 Unknowns relating to treatment benefits

Limited data exist on the effect of dose increases from 400 mg to 600 mg or 800 mg in patients with cancer of stomach or gut. The safety and effectiveness of imatinib in children with MDS/MPD, DFSP, GIST and HES/CEL aged less than 18 years of age have not been established in studies.

There are limited information on the use of imatinib in pregnant women. Studies in animals have however shown reproductive harmful effects and the potential risk for the unborn baby

is not known. Imatinib should not be used during pregnancy unless clearly necessary. If it is used during pregnancy, the patient must be informed of the potential risk to the unborn baby.

There is limited information on imatinib distribution in human milk. Studies in two breast-feeding women showed that both imatinib and its active substance can be distributed into human milk. Considering the combined amount of imatinib and the metabolite (breakdown substance) and the maximum daily milk intake by new born babies, the total exposure would be expected to be low. However, since the effects of low-dose exposure of the new born to imatinib are not known, women taking imatinib should not breast-feed the new born.

VI.2.4 Summary of safety concerns

Important identified risks		
Risk	**What is known**	**Preventability**
Decreased bone marrow activity (myelosuppression)	Myelosuppression is a condition in which bone marrow activity is decreased, resulting in fewer red blood cells, white blood cells, and platelets. Treatment of leukaemia (cancer of blood or bone marrow which produces blood cells) with imatinib has been associated with low count of white blood cells (neutropenia) or low amount of platelets (thrombocytopenia). Occurrence of myelosuppression with imatinib may increase on simultaneous treatment with chemotherapy (medicines used to kill cancer cells)	These events can usually be managed with either a reduction of the dose or a temporary stoppage of treatment, but in rare cases can lead to permanent stop of treatment. Special care is required for use of imatinib in combination with other medicines. Complete blood count tests should be done regularly during treatment with imatinib.
Abnormal collection of watery fluid (oedema and fluid retention)	Oedema is the abnormal collection of fluid below the skin and in the cavities of the body. Imatinib may cause body to retain water (serious fluid retention). Collection of fluid surrounding lungs (pleural effusion), oedema, collection of fluid in lungs (pulmonary oedema), collection of fluid in space between lining of stomach abdomen and organs (ascites) and superficial oedemas like puffy eyes (periorbital oedema) or swelling around ankles (lower limb oedemas) has been reported in patients taking imatinib.	These side effects can usually be managed by stopping imatinib for short term or by reducing the dose of imatinib and with water pills (diuretics) and other proper supportive care measures. It is advised that patients should be weighed regularly. Patient should inform the treating doctor immediately if he/she experience unexpected rapid weight gain and should be carefully checked for weight gain.
Bleeding in brain, stomach or gut (CNS and GI haemorrhage)	In patients with tumour in stomach or gut (GIST), risks of bleeding have been reported with the use of imatinib.	Standard practices and procedures for the observing and management of bleeding in all patients should be applied. When needed, stoppage of imatinib treatment may be considered.
Blockage, hole and ulcers in stomach or gut lining (GI obstruction, perforation, ulceration)	Ulcers in mouth and stomach are uncommon (may affect up to 1 in 100 treated people) side effects reported with use of imatinib. Blockage of gut (ileus/intestinal obstruction), development of hole through wall of food pipe,	Patient should contact the treating doctor if he/she develops any of these problems

	stomach or gut (gastrointestinal perforation) are the side effects reported with not known frequency with use of imatinib	
Harmful effects on liver (hepatotoxicity)	Cases of liver injury, including liver failure and death of liver cells (hepatic necrosis), have been observed with imatinib. When imatinib is combined with high dose chemotherapy (medicines used to kill cancer cells, an increase in serious liver reactions has been detected. Increased harmful effects on liver are reported on simultaneous use of medicine used to treat cancer (L-asparaginase) with imatinib.	Patient should inform the treating doctor/pharmacist before taking imatinib, if he/she has liver related problems. Liver function should be carefully observed in circumstances where imatinib is combined with chemotherapy. Special care is advised for use of imatinib in combination with other medicines.
Skin rashes and serious skin reactions (skin rashes and severe cutaneous reactions)	Patient allergic to imatinib or any of the content of the medicinal product develops skin reactions. Rash, red skin with blisters on the lips, eyes, skin or mouth, peeling skin, fever, raised red or purple skin patches, itching, burning sensation, pustular eruption (signs of skin problems) are not common (may affect up to 1 in 100 treated people) side effects reported with the use of imatinib. Itching, redness of skin, dry skin and decreased or increased skin sensitivity to sunlight (photosensitivity) are common (may affect up to 1 in 10 treated people) side effects reported with use of imatinib. Serious skin reactions (Acute febrile neutrophilic dermatosis (Sweet's syndrome), angioneurotic oedema, rash vesicular, erythema multiforme, leucocytoclastic vasculitis, Stevens-Johnson syndrome, acute generalised exanthematous pustulosis (AGEP)) are rare (may affect up to 1 in 1000 treated people) side effects reported with use of imatinib. Reddening and/or swelling on the palms of the hands and soles of the feet which may be accompanied by tingling sensation and burning pain are side effects reported with not known frequency with use of imatinib.	Patient should inform treating doctor if he/she develops any type of skin reactions.
Underactive thyroid gland (hypothyroidism)	It is a condition in which the body lacks sufficient thyroid hormone. Cases of hypothyroidism have been reported in patients in whom thyroid gland has been removed and taking simultaneous treatment with levothyroxine and imatinib.	Thyroid-stimulating hormone (TSH) levels should be closely monitored in such patients. Patients should be advised to inform the treating doctor, if he/she is taking the medicine levothyroxine because of removal of thyroid gland.

Low amount of phosphate in blood (hypophosphatemia)	Hypophosphatemia is an electrolyte (a compound that can conduct an electric current) disturbance in which there is an abnormally low amount of phosphate in the blood. This reaction have been reported with use of imatinib in clinical studies with not common frequency (may affect up to 1 in 100 treated people).	Patient should inform the treating doctor if he/she develops hypophosphatemia. .
Heart failure (cardiac failure)	In patients with hypereosinophilic syndrome (blood problem in which some blood cells (named eosinophils) start growing out of control) cases of failure of heart to pump enough blood (cardiogenic shock/left ventricular dysfunction) have been associated with imatinib treatment. Heart failure (congestive heart failure) is a not common (may affect up to 1 in 100 treated people) and heart attack (myocardial infarction) and chest pain (angina) are rare (may affect up to 1 in 1000 treated people) side effects reported with use of imatinib	Patients should inform the treating doctor or pharmacist if he/she has heart related problems. Patients with heart disease or heart failure history should be observed carefully and any signs of heart failure should be checked and treated.
Loss of kidney function (acute renal failure)	In patients with kidney problems, presence of amount of imatinib in blood may be on higher side as compared to person with normal individuals.	Patients should inform the treating doctor or pharmacist if he/she has kidney related problems. Patients with history of kidney failure should be observed carefully and any patients with signs of kidney failure should be checked and treated. Patients with kidney problems should be given minimum starting dose of imatinib. Patients with serious kidney problems should be treated with care. The dose can be reduced if not tolerated by the patient.
Serious breathing side effects (Severe respiratory adverse reactions)	Events like cough, having difficulty breathing or painful breathing (signs of lung problems) have been reported in patients administered with imatinib. Scarring of the lungs (pulmonary fibrosis), increase in blood pressure in blood vessels of lungs (pulmonary hypertension), bleeding from lungs (pulmonary haemorrhage) are rare (may affect up to 1 in 1000 treated people) side effects reported with use of imatinib. Breathing failure associated with the use of imitinib is reported with not known frequency.	Patients should be advised to inform the treating doctor immediately if such types of reactions are experienced.
Destruction of skeletal muscle and disturbed skeletal muscle function (rhabdomyolysis and myopathy)	Imatinib has been reported to cause muscle spasms (a sudden, violent, involuntary muscular contraction) with fever, red-brown urine, pain or weakness in muscles (signs of muscle problems). Rhabdomyolysis and myopathy are rare (may	Patients should be advised to inform the treating doctor immediately if he/she develops muscle problems.

	affect up to 1 in 1000 treated people) side effect associated with the use of imatinib.	
Cyst or bleeding in ovaries (ovarian haemorrhage and haemorrhagic ovarian cyst)	Pelvic pain sometimes with nausea and vomiting, with unexpected vaginal bleeding, feeling dizzy or fainting due to low blood pressure (signs of problems with ovaries or womb) have been reported with use of imatinib. Ovarian haemorrhage and haemorrhagic ovarian cyst are rare (may affect up to 1 in 1000 treated people) side effects reported with use of imatinib.	Patient should inform doctor if he/she experiences such type of side effects.
A serious condition that can happen when cancer treatment causes cancer cells to die quickly (tumor lysis syndrome)	Tumour lysis syndrome (TLS) is a serious condition that can happen when cancer treatment causes cancer cells to die quickly. TLS is rare (may affect up to 1 in 1000 treated people) side effects reported with use of imatinib.	Correction of lack of water in body (dehydration) and treatment of high uric acid amount in blood are advised before starting treatment with imatinib. Patients should be advised to inform the treating doctor immediately if such type of side effect is experienced.
Slowing of growth in children (Growth retardation in children)	Cases of growth retardation in children are reported with imatinib with not known frequency.	Close observation of growth in children under imatinib treatment is advised.
Simultaneous use with CYP3A4 inhibitors (Interaction with strong CYP3A4 inhibitors)	Simultaneous use of medicines that stops the breakdown of imatinib (CYP3A4 inhibitors) such as medicines used for human immuno deficiency virus (HIV) infection (indinavir, lopinavir, ritonavir, saquinavir, telaprevir, nelfinavir, boceprevir); medicines used to treat fungal infection (including ketoconazole, itraconazole, posaconazole, voriconazole) and antibiotics like erythromycin, clarithromycin and telithromycin leads to increase blood amount of imatinib leading to increase in its effect.	Care should be taken when giving imatinib simultaneously with inhibitors of cytochrome P450 (CYP) 3A4 family. Patients should be advised to inform doctor before starting treatment with imaitnib regarding if already taking, have recently taken or might take any other medicines, including medicines obtained without a prescription (such as paracetamol) and including herbal medicines.
Simultaneous use with CYP3A4 inducers (Interaction with strong CYP3A4 inducers)	Simultaneous use of medicines that increases the breakdown of imatinib (CYP3A4 inducers) (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital, fosphenytoin, primidone or *Hypericum perforatum*, also known as St. John's Wort) may reduce the imatinib effect.	Simultaneous use of imatinib with CYP3A4 inducers should be avoided. Patients should be advised to inform doctor before starting treatment with imaitnib regarding if already taking, have recently taken or might take any other medicines.
Simultaneous use with the medicines removed or excreted by	Simultaneous use of imatinib with CYP3A4 substrates like simvastatin (medicine used to lower cholesterol amount) leads to blockage of	Patients should be advised to inform doctor before starting treatment with imaitnib regarding if

CYP3A4 (Interaction with drugs eliminated by CYP3A4)	CYP3A4. Simultaneous use of imatinib with CYP3A4 substrates with narrow therapeutic window (safe dose range of medicine in which effect is obtained) e.g cyclosporine, pimozide, tacrolimus, sirolimus, ergotamine, diergotamine, fentanyl, alfentanil, terfenadine, bortezomib, docetaxel and quinidine can cause increase in their blood levels.	already taking, have recently taken or might take any other medicines.

Important potential risks	
Risk	**What is known (Including reason why it is considered a potential risk)**
Development of new types of cancers (second malignancies in survivors)	Patients treated with imatinib may be at an increased risk of developing new cancers. There are theoretical mechanisms and more patients treated with imatinib developed new cancers than those not treated with imatinib, but this could also be due to the fact that they live longer.
Bleeding (disseminated intravascular coagulation)	Patients treated with imatinib may be at an increased risk of bleeding. Normal clotting is disturbed and serious bleeding can occur from various sites. Patients who require treatment which reduce the ability of the blood to clot should be treated with particular type of treatment (low molecular weight or standard heparin) in place of blood thinners like warfarin belonging to coumarin class.
Tolerability during pregnancy and pregnancy outcomes	There is limited data available on the use of imatinib in pregnant women. Patients should be advised to inform doctor if may be or may become pregnant or are planning to have a baby before taking imatinib. Imatinib is not recommended during pregnancy unless clearly necessary as it may harm the baby. Doctor should discuss the possible risks of taking imatinib during pregnancy. Women who might become pregnant are advised to use effective contraception (birth control measures) during treatment with imatinib. Patients who are concerned about their fertility while taking imatinib should be advised to consult with treating doctor.
Simultaneous use of imatinib with medicines removed by CYP2D6 substrates (interaction with drugs eliminated by CYP2D6)	Drug interaction occurs with the simultaneous use of imatinib with CYP2D6 substrates such as metoprolol (medicine used to treat chest pain). Patients should be closely observed and care should be taken when given imatinib with CYP2D6 substrates.
Simultaneous use of imatinib with medicines used for pain relief (acetaminophen/paracetamol) (interaction	Drug interaction occurs with the simultaneous use of imatinib with acetaminophen/paracetamol (medicines used to treat pain). Care should therefore be taken when using high doses of imatinib and paracetamol simultaneously.

with acetaminophen/paracetamol)	
Hypoglycaemia	There is a lack of conclusive data indicating any causal relationship at this time13.
Suicidality	There is a lack of conclusive data indicating any causal relationship at this time13.

Missing information	
Risk	**What is known**
Use in children (paediatric use)	Slowing of growth (growth retardation) has been seen in children and children about to be teen ager (pre-adolescents) receiving imatinib. Effect of imatinib on long term treatment is not known. Therefore, close observation of growth in children under imatinib treatment is advised.
Use in children below 2 years of age (Paediatric patients below 2 years of age)	Use of imatinib in new born babies (below 2 years of age) is not known.
Use in elderly patients	No dose adjustments are necessary in patients over 65 years of age. There are no studies on the use of imatinib inolder patients.
Renal impairment	Patients with renal dysfunction or on dialysis should be given the minimum recommended dose of 400 mg daily as starting dose. However, in these patients caution is recommended. The dose can be reduced if not tolerated. If tolerated, the dose can be increased for lack of efficacy.
Hepatic impairment	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.

VI.2.5 Summary of additional risk minimisation measures by safety concern

All medicines have a 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.

VI.2.6 Planned post authorisation development plan

Not applicable

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

Table 1: Major changes to the Risk Management Plan over time			
Version	**Date**	**Safety Concerns**	**Comment**
1.0	16-April-2014	**Important identified risks:**	NA

		• Myelosuppression • Oedema and Fluid Retention • Central Nervous System (CNS) and Gastro-intestinal (GI) Haemorrhages • Gastrointestinal Obstruction, Perforation or Ulceration • Hepatotoxicity • Skin Rashes and Severe Cutaneous Reactions • Hypothyroidism • Hypophosphataemia • Cardiac Failure • Acute Renal Failure • Severe Respiratory Adverse Reactions • Rhabdomyolysis and Myopathy • Ovarian haemorrhage and haemorrhagic ovarian cyst • Tumour lysis syndrome (TLS) • Growth retardation in children • Interaction with strong Cytochrome P (CYP) 3A4 inhibitors • Interaction with strong CYP3A4 inducers • Interaction with drugs eliminated by CYP3A4 **Important potential risks:** • Second Malignancies in Survivors • Disseminated Intravascular Coagulation • Tolerability during Pregnancy and Pregnancy Outcomes • Interaction with drugs eliminated by CYP2C9, CYP2C19 and CYP2D6 • Interaction with acetaminophen/paracetamol **Missing information:** • Paediatric patients: Long term follow up • Paediatric patients below 2 years of age • Use in elderly patients	
2.0	01-March-2016	**Important identified risks:** • Myelosuppression • Oedema and Fluid Retention • Central Nervous System (CNS) and Gastro-	Modified in line with the assessors comment.

		intestinal (GI) Haemorrhages • Gastrointestinal Obstruction, Perforation or Ulceration • Hepatotoxicity • Skin Rashes and Severe Cutaneous Reactions • Hypothyroidism • Hypophosphataemia • Cardiac Failure • Acute Renal Failure • Severe Respiratory Adverse Reactions • Rhabdomyolysis and Myopathy • Ovarian haemorrhage and haemorrhagic ovarian cyst • Tumour lysis syndrome (TLS) • Growth retardation in children • Interaction with strong Cytochrome P (CYP) 3A4 inhibitors • Interaction with strong CYP3A4 inducers • Interaction with drugs eliminated by CYP3A4 **Important potential risks:** • Second Malignancies in Survivors • Disseminated Intravascular Coagulation • Tolerability during Pregnancy and Pregnancy Outcomes • Interaction with drugs eliminated by CYP2C9, CYP2C19 and CYP2D6 • Interaction with acetaminophen/paracetamol • Hypoglycaemia • Suicidality **Missing information:** • Paediatric patients: Long term follow up • Paediatric patients below 2 years of age • Use in elderly patients • Renal impairment • Hepatic impairment	