VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

1. Myelodysplastic/myeloproliferative diseases (MDS/MPD).

The bone marrow functions as a factory that manufactures three kinds of blood cells: red blood cells, white blood cells, and platelets. Myelodysplastic Syndromes (MDS) are a group of diverse bone marrow disorders in which the bone marrow does not produce enough healthy blood cells. MDS is primarily a disease of the elderly (most patients are older than age 65), but MDS can affect younger patients as well. Healthy bone marrow produces immature blood cells — called stem cells, progenitor cells, or blasts — that normally develop into mature, fully functional red blood cells, white blood cells, and platelets. In MDS, these stem cells may not mature and may accumulate in the bone marrow or they may have a shortened life span, resulting in fewer than normal mature blood cells in the circulation.
The incidence of MDS/MPN varies widely, ranging from approximately 3 per 100,000 individuals older than 60 years annually to as few as 0.13 per 100,000 children from birth to 14 years annually.

2. Hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia

The hypereosinophilic syndrome (HES) is characterized by the presence of marked unexplained blood and tissue eosinophilia associated with a variety of clinical manifestations. Red blood cells count more than 1.5 x 10^9/L (for more than 6 months) (Hypereosinophilic syndrome) is rare with only 50 cases between 1971 and 1982, being even rarer in children. HES can present anywhere from the age of 20 to 70 years, with a mean age of presentation of 33 years. HES is more common in males (9:1). [1]

2. Gastrointestinal stromal tumours (GIST).

Gastrointestinal stromal tumours (tumour of digestive tract) are rare. They represent 0.1 to 3patients out of 100 of all gastrointestinal cancers. There are approximately 900 new cases per year in the UK. They can occur in either sex and at any age but 75% are diagnosed in patients above 50 years of age. [1]

3. Dermatofibrosarcoma protuberans (DFSP).

Dermatofibrosarcoma protuberans (DFSP) is a rare infiltrating soft tissue cancer arising from the skin. They are more frequent in women than in men (ratio of 4:1). They can occur at any age, most commonly in young adulthood. [1]

4. Chronic myeloid leukaemia (**CML)**

Chronic myeloid leukaemia (CML) is a cancer of the white blood cells. Over time, the white blood cellsgrow abnormally due to increased production. . The annual incidence of CML is between 1 and 2 cases per 100,000. CML represents about 14% of all leukaemias. It can occur at any age; however, it is rare in children occurring. The median age at diagnosis is 60-65 years. [1]

5. Acute Lymphoblastic leukemia (**ALL)**

Acute Lymphoblastic leukemia is a sudden onset, rapidly progressing form of cancer of blood-forming cells that is characterized by the presence in the blood and bone marrow of large numbers of unusually immature white blood cells. It can occur at any age, but about 6 in 10 cases occur in children. It occurs in about 450 children in the UK each year. It can occur at any age in childhood, but most commonly develops between the ages of 4 and 7 years. Boys are more commonly affected than girls. It is less common in adults. It affects around 200 adults in the UK each year. The average age of an adult with ALL is 55 years. Global incidence is about 3 per 100,000 population, with about 3 out of 4 cases occurring in children aged under 6 years. [1]

VI.2.2 Summary of treatment benefits

Imatinib is approved to treat a rare cancer called Chronic Myeloid Leukemia (CML). Gleevec is approved to treat a rare cancer called Chronic Myeloid Leukemia (CML). 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. It is hoped that Gleevec has fewer serious side effects than other cancer drugs.

VI.2.3 Unknowns relating to treatment benefits

The safety and efficacy of Imatinib in children below 2 years of age, use in elderly population and patients with renal impairment and hepatic impairment have not been established.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is it known	Preventability
Interaction with CYP3A4 inducers, inhibitors and substrates	Some medicines can interfere with the effect of imatinib when taken together. They may increase or decrease the	Yes, As per section 2 of PIL and section 4.2 of SPC the patient should tell their doctor or pharmacist if they are taking, have recently taken or might take

Risk	What is it known	Preventability
	effect of imatinib, either leading to increased side effects or making imatinib less effective. Imatinib may do the same to some other medicines.	any other medicines, including medicines obtained without a prescription (such as paracetamol) and including herbal medicines (such as St. John's Wort). The patient should tell their doctor, if they are using medicines that prevent the formation of blood clots.
Deficient activity of the thyroid gland. (Hypothyroidism)	Cases of less activity of the thyroid gland (hypothyroidism) have been reported in case of surgical removal of the thyroid gland (thyroidectomy) and in patients using medicine to treat deficient activity of the thyroid gland (levothyroxine replacement) during treatment with imatinib.	Yes, As per section, 4.2 of SPC, Thyroid stimulating hormone (TSH) levels should be checked regularly in such patients. As per section 2 (What you need to know before you take imatinib capsules), the patient should talk to doctor before taking imatinib capsules, if the patient's are taking the medicine levothyroxine because their thyroid has been removed.
Liver toxicity (Hepatotoxicity)	Breakdown of (Metabolism) of imatinib is mainly via liver (hepatic), and only 13% of removal of waste products from the body (excretion) is through the kidneys. Cases of liver injury, including failure of liver to function (hepatic failure) and liver cell death (hepatic necrosis), have been observed with imatinib.	Yes, as per section 2 and section 4 of PIL, The patient should talk to their doctor before taking imatinib capsules, if they have or have ever had a liver problem. The risk is mentioned in section 4. Some side effects may be serious. The patient should tell their doctor straight away if they get any of the following: Feeling

Risk	What is it known	Preventability
	When imatinib is combined with high dose chemotherapy regimens, an increase in serious hepatic reactions has been detected. Hepatotoxicity with Uncommon frequency (may affect up to 1 in 100 people) or rare frequency (may affect up to 1 in 1,000 people) has been observed while being treated with Imatinib.	sick (nausea), with loss of appetite, dark-coloured urine, yellow skin or eyes (signs of liver problems).
bodyweight gain due to water retaintion (oedema and fluid retention)	Imatinib may cause accumulation of fluid in the body. This side effect is common (may affect up to 1 in 10 people) and very common Very common (may affect more than 1 in 10 people)	Yes, as per section 2 and section 4 of PIL, it is highly recommended that patients weight should be regularly checked. As per section 4, the patient should tell doctor straight away if they get Rapid weight gain. Imatinib may cause patients body to retain water (severe fluid retention).
Bleeding in stomach and intestine (Gastrointestinal haemorrhage)	Bleeding in stomach and intestine (Gastrointestinal haemorrhage) (Severe stomach pain, blood in vomitting, stools or urine, black stools (signs of gastrointestinal disorders) with Uncommon frequency (uncommon (≥1/1,000 to <1/100) has been observed while being treated with Imatinib.	Yes, as per section 4 of PIL, The patient should tell doctor straight away if they get Stomach pain with feeling sick (nausea) or Severe abdominal pain, blood in vomit, stools or urine, black stools (signs of gastrointestinal disorders). As per section 3, the patient should take imatinib

Risk	What is it known	Preventability
	Yes Imatinib may cause bleeding in stomach and intestine. This is **Uncommon** (may affect up to 1 in 100 people) **or rare** (may affect up to 1 in 1,000 people):	capsules with a meal. This will help protect patient from stomach problems when taking imatinib capsules.
Abnormal release of large quantities of cellular components into the blood following the rapid lysis of cancerous cells (Tumor lysis syndrome)	Imatinib may cause Abnormal release of large quantities of cellular components into the blood following the rapid lysis of cancerous cells This is with rare frequency (≥1/10,000 to <1/1,000) while being treated with Imatinib.	As per section 4 of PIL the patient should tell the doctor, if they experience any of the following. Nausea, shortness of breath, irregular heartbeat, clouding of urine, tiredness and/or joint discomfort associated with abnormal laboratory test results (eg. high potassium, uric acid and calcium levels and low phosphorous levels in the blood).
Decrease in the production of cells that produce immunity, carry oxygen and those responsible for blood clotting (Bone marrow depression)	Imatinib may cause decrease in the production of cells that producr immunity, carry oxygen and those responsible for blood clotting. This is with uncommon frequency (≥1/1,000 to < 1/100) has been observed while being treated with Imatinib.	Yes, as per section 4 of PIL , decrease in the production of cells that produce immunity, carry oxygen and those responsible for blood clotting can occur. The patient should tell doctor if they experience Pale skin, feeling tired and breathlessness and having dark urine (signs of low levels of red blood cells).
Swelling in brain or skull (CNS	The risk of bleeding and cerebral haemorrhage have been observed	Yes, as per section 4 of PIL, the patient should tell their doctor if

Risk	What is it known	Preventability
haemorrhages)	with Imatinib. This occurs Uncommonly (may affect up to 1 in 100 people) or rarely (may affect up to 1 in 1,000 people):	they experience Severe headache, weakness or paralysis of limbs or face, difficulty speaking, sudden loss of consciousness (signs of nervous system problems such as bleeding or swelling in skull/brain).
Bleeding in lungs (Severe Respiratory Adverse Reactions)	Bleeding in lungs (Severe Respiratory Adverse Reactions) has been observed with Imatinib.	As per section 4 of PIL, the patient should tell doctor if they experience cough, difficulty in breathing or painful breathing (signs of lung problems).
Liver cells death (Hepatic necrosis)	Liver cells death (Hepatic necrosis) has been observed with Imatinib. This is Uncommon (may affect up to 1 in 100 people) or rare (may affect up to 1 in 1,000 people):	As mentioned in section 2 of PIL, the patient should tell their doctor before taking imatinib capsules if they have or have ever had a liver, problem. The patient should tell their doctor if they experience any of the following: Feeling sick (nausea), with loss of appetite, dark-coloured urine, yellow skin or eyes (signs of liver problems).
Severe inflammatory eruption of the skin (Skin Rashes and Severe Cutaneous Adverse Reactions (SCARs))	Severe inflammatory eruption of the skin (Skin Rashes and Severe Cutaneous Adverse Reactions (SCARs)) has been observed with Imatinib. This is Uncommon (may affect up to 1 in 100 people) or	As mentioned in section 4 possible side effects, the patient should tell their doctor if they experience rash, red skin with blisters on the lips, eyes, skin or mouth, peeling skin, fever, raised

Risk	What is it known	Preventability
	rare (may affect up to 1 in 1,000 people).	red or purple skin patches, itching, burning sensation, pustular eruption (signs of skin problems).
Obstruction of the passage of intestinal contents, formation of hole in the stomach or ulcer in the stomach (Gastrointestinal Obstruction, Perforation, or Ulceration)	Yes, Imatinib may cause Obstruction of the passage of intestinal contents, formation of hole in the stomach or ulcer in the stomach.	The risk of Obstruction of the passage of intestinal contents, formation of hole in the stomach or ulcer in the stomach has been mentioned in section 4 (possible side effects) of PIL. The patient should tell their doctor if they experience Feeling sick (nausea) with diarrhoea and vomiting, abdominal pain or fever (signs of bowel problems). Severe abdominal pain, blood in your vomit, stools or urine, black stools (signs of gastrointestinal disorders).
Low level of phosphorus in blood (Hypophosphatemia)	Imatinib may cause decrease in level of phosphorus in blood.	The risk of Hypophosphatemia has been mentioned in section 4 of PIL. The patient should tell their doctor, if they experience Nausea, shortness of breath, irregular heartbeat, clouding of urine, tiredness and/or joint discomfort associated with abnormal laboratory test results (eg. high potassium, uric acid and calcium levels and low phosphorous levels in the blood).

Risk	What is it known	Preventability
Heart failure (Cardiac Failure)	Imatinib may cause heart failre. This is Uncommon (may affect up to 1 in 100 people) or rare (may affect up to 1 in 1,000 people).	As per section 2 (and section 4 of PIL, the patient should talk to the doctor, if they have or ever had heart problem. The patient should tell their doctor, if they experience Chest pain, irregular heart rhythm (signs of heart problems).
Sudden onset kidney failure (Acute Renal Failure)	Imatinib may cause Sudden onset kidney failure. This is Uncommon (may affect up to 1 in 100 people) or rare (may affect up to 1 in 1,000 people).	As per section 2 and section 4 of PIL, the patient should talk to the doctor, if they have or ever had kidney problem. The patient should tell their doctor straight away if they have severely decreased urine output, feeling thirsty (signs of kidney problems).
Rapid destruction of muscle and diseases of muscle (Rhabdomyolysis) and Myopathy)	Yes. Imatinib may cause Rapid destruction of skeletal muscle and diseases of muscle.	As per section 4 of PIL and section 4.8 of SPC The patient should tell their doctor straight away, if they experience muscle spasms with fever, red-brown urine, pain or weakness in muscles. The risk of Rhabdomyolysis has been mentioned in section 4.8 of SPC and section 4 (possible side effects) of PIL.
Bleeding from ovary and collection of fluid, surrounded by a very thin wall,	Imatinib may cause bleeding from ovary and collection of fluid, surrounded by a very thin wall, within an ovary.	The risk of Ovarian Hemorrhage and Hemorrhagic Ovarian Cyst has been mentioned in section 4 of PIL. The patient should tell

Risk	What is it known	Preventability
within an ovary. (Ovarian Hemorrhage and Hemorrhagic Ovarian Cyst)	This is Uncommon (may affect up to 1 in 100 people) or rare (may affect up to 1 in 1,000 people):	their doctor straight away, if they experience Pelvic pain sometimes with nausea and vomiting, with unexpected vaginal bleeding, feeling dizzy or fainting due to low blood pressure (signs of problems with your ovaries or womb).
Growth retardation in children	The frequency is not known	As per section 2 and section 4 of PIL, Some children and adolescents taking imatinib may have slower than normal growth. The doctor should monitor the growth at regular visits

Important potential risks

Risk	What is known
Tolerability during Pregnancy and Pregnancy Outcome	Imatinib should not be used in pregnant and breast feeding female patients. Pregnancy There are limited data on the use of imatinib in pregnant women. Studies in animals have however shown harmful effects on reproduction and the potential risk for the unborn baby (foetus) is unknown. Imatinib should not be used during pregnancy unless clearly necessary. This risk has been mentioned in Section 4.6 of the SPC and section 2 of PIL.

Risk	What is known
Development of new cancer in patient who survives (Second Malignancies in Survivors)	In the view of limited evidence on association of the risk with Imatinib. On receipt of additional information the same would be communicated through the SPC, PIL and additional risk minimization activities may be proposed if necessary.
Rare, life-threatening condition that prevents blood from clotting (Disseminated Intravascular Coagulation)	In the view of limited evidence on association of the risk with Imatinib. On receipt of additional information the same would be communicated through the SPC, PIL and additional risk minimization activities may be proposed if necessary.
Low blood sugar (Hypoglycaemia)	In the view of limited evidence on association of the risk with Imatinib. On receipt of additional information the same would be communicated through the SPC, PIL and additional risk minimization activities may be proposed if necessary.
Increase tendency for suicide (Suicidality)	In the view of limited evidence on association of the risk with Imatinib. On receipt of additional information the same would be communicated through the SPC, PIL and additional risk minimization activities may be proposed if necessary.

Missing information

Risk	What is known
Use in children below 2 years of age	There is no experience with the treatment of children below 2 years of age.

	This information has been mentioned in Section 4.2 of the SPC and section 2 of PIL.
Kidney disease (Renal impairment)	Patients with renal impairment should be given the minimum starting dose. Patients with severe kidney disease should be treated with caution. The dose can be reduced if not tolerated. This information has been mentioned in 4.4 (Special warnings and precautions for use) of SPC.
Liver disorder (Hepatic impairment)	. In patients with liver disorder (mild, moderate or severe), blood test and liver function tests should be carefully checked. 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 of cancer treatment (chemotherapy regimens), an increase in serious liver reactions has been detected. Liver function should be carefully checked in circumstances where imatinib is given with cancer treatment also known to be associated with hepatic dysfunction.
Elderly patients	Imatinib's movement of drugs within the body (pharmacokinetics) have not been specifically studied in older people. No specific dose recommendation is necessary in older people. This risk is mentioned in section 4.2 (Posology and method of administration)
Follow up for long time in children	The long-term effects of prolonged treatment

(Paediatric patients – long term follow up)	with imatinib on growth in children are unknown. Therefore, children who are on Imatinib should be followed for long time.

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

These additional risk minimisation measures are for the following risks:

Safety concern in lay terms (medical term)

Risk minimisation measure(s): None
Objectives and rationale: Not applicable
Summary description of main additional risks minimisation measures: Not applicable

VI.2.6 Planned post authorisation development plan

Not applicable.

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

Version	Date	Safety concerns	Comment
02	20-Apr-2015	Summary of RMP revised	Not applicable