VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

CML (chronic myeloid leukaemia) is a malignant disease that usually begin in the bone marrow and results in high numbers of abnormal white blood cells, which stop the healthy blood cells from performing their activities, leading to symptoms such as bleeding and bruising, feeling very tired, and increased risk of infections. CML incidence is relatively consistent in all countries where adequate statistics are available. Occurring at about 1 to 2 per 100,000 population, CML is a rare disease in children, where it makes up no more than 5% of the leukaemias.

In adults, CML represents about 15% of all cases of leukaemia and is less common than acute myeloid leukaemia and myelodysplastic syndrome (AML/MDS) and chronic lymphocytic leukaemia (CLL).

The median age of onset is 45 to 55 years. Half of CML patients are older than 60 years (ref. 1).

ALL (acute lymphoblastic leukaemia) is a malignant disease of the white blood cells, characterized by the increased production of cancerous, immature white blood cells, which continuously multiply, causing damage and death by inhibiting the production of normal cells—such as red and white blood cells and platelets—in the bone marrow and by spreading to other organs.

The symptoms of ALL are indicative of a reduced production of functional blood cells, because the leukemia wastes the resources of the bone marrow, which are normally used to produce new, functioning blood cells. These symptoms can include fever, increased risk of infection, increased tendency to bleed and signs indicative of anaemia including pallor, high heart rate, fatigue and headache.

The hypereosinophilic syndrome (HES) is a disease characterized by a persistently elevated eosinophil count (a type of white blood cells) in the blood for at least six months without any recognizable cause, with involvement of either the heart, nervous system, or bone marrow.

Chronic eosinophilic leukqaemia (CEL) is a disease in which too many eosinophils (a type of white blood cells) are found in the bone marrow, blood, and other tissues. CEL may stay the same for many years, or it may progress quickly to acute leukemia.

VI.2.2 Summary of treatment benefits

In 1960, it was discovered that patients with leukemia had a small chromosome 22, and this came to be identified as the Philadelphia chromosome. By the late 1980s, researchers learned that this chromosome abnormality produced an abnormal protein, bcr-abl, which ultimately

caused leukemia, and during the early 1990s testing was conducted to find compounds that would block the function of this protein. Early testing found that the compound known as STI571 showed an inhibitory effect on the bcr-abl protein, and small clinical trials investigating this compound were commenced. The results of the initial study were so promising (all 31 of the patients receiving doses of at least 300 mg daily experienced a normalization of blood counts), that larger studies were initiated. In early 2001, Novartis submitted NDA #02133510 to the FDA for approval of their compound STI571, now named Gleevec. The FDA approved Gleevec® for the indication of chronic myeloid leukemia after just 2 and a half months of review, the fastest any drug has been approved by the FDA. A few months later, the EU approved the sale and marketing of Glivec® (imatinib mesilate) in November 2001 (ref. 2).

VI.2.3 Unknowns relating to treatment benefits

There is limited experience with imatinib use in children below 2 years of age and during long term treatment, in patients with renal and hepatic impairment and in elderly patients.

VI.2.4 Summary of safety concerns

Important Identified Risks

Risks with imatinib	What is known	Preventability
Myelosuppression (a disorder caused by severely decreased production of blood cells)	Imatinib can reduce the number of white blood cells, so patients might get infections more easily, with symptoms such as fever, severe chills, sore throat or mouth ulcers, unexpected bleeding or bruising.	By monitoring early symptoms. The patient should consult the doctor if any of these symptoms occur.
Oedema and fluid retention (accumulation of body fluid)	Imatinib may cause the body to retain water (severe fluid retention), leading to rapid weight gain.	By monitoring early symptoms. The patient should consult the doctor if fluid retention occurs.
CNS and GI haemorrhages (brain and digestive system bleedings)	Some patients receiving treatment with imatinib may experience severe headaches, 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) or severe abdominal pain, blood in your vomit, stools or urine, black stools (signs of gastrointestinal disorders).	By monitoring early symptoms. The patient should consult the doctor if any of the symptoms occur.
Gastrointestinal obstruction, perforation or ulceration	Some patients receiving treatment with imatinib may	By monitoring early symptoms. The

Risks with imatinib	What is known	Preventability
	experience feeling sick (nausea) with diarrhoea and vomiting, abdominal pain or fever (signs of bowel problems), pain or swelling of the abdomen, flatulence, heartburn or constipation.	patient should consult the doctor if any of the symptoms occur.
Hepatotoxicity (liver toxicity)	Some patients receiving treatment with imatinib may experience feeling sick (nausea), with loss of appetite, dark-coloured urine, yellow skin or eyes (signs of liver problems).	By monitoring early symptoms. The patient should consult the doctor if any of the symptoms occur.
Skin rashes and severe cutaneous reactions (SCARs)	Some patients receiving treatment with imatinib may experience 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).	By monitoring early symptoms. The patient should consult the doctor if any of the symptoms occur.
Hypothyroidism (decrease blood level of thyroid hormone)	Some patients receiving treatment with imatinib may experience swelling such as round your ankles or puffy eyes, weight gain.	By monitoring early symptoms. The patient should consult the doctor if any of the symptoms occur.
Hypophosphataemia (decreased blood level of phosphates)	Some patients receiving treatment with imatinib may experience muscle dysfunction and weakness, respiratory depression due to respiratory muscle weakness, mental status changes, instability of cell membranes	By monitoring early symptoms. The patient should consult the doctor if any of the symptoms occur.
Cardiac failure	Some patients receiving treatment with imatinib may experience chest pain, irregular heart rhythm (signs of heart problems)	By monitoring early symptoms. The patient should consult the doctor if any of the symptoms occur.
Acute renal failure	Some patients receiving treatment with imatinib may experience severely decreased	By monitoring early symptoms. The patient should consult the doctor if

Risks with imatinib	What is known	Preventability
	urine output, feeling thirsty (signs of kidney problems).	any of the symptoms occur.
Severe respiratory adverse reactions	Some patients receiving treatment with imatinib may experience congestion, either in the nasal sinuses or lungs, runny nose, cough, sore throat, body aches, fatigue, high fever and chills, difficulty breathing.	By monitoring early symptoms. The patient should consult the doctor if any of the symptoms occur.
Rhabdomyolysis and myopathy (breakdown of muscle fibers)	Some patients receiving treatment with imatinib may experience muscle spasms with a fever, red-brown urine, pain or weakness in your muscles (signs of muscle problems).	By monitoring early symptoms. The patient should consult the doctor if any of the symptoms occur.
Ovarian haemorrhage and haemorrhagic ovarian cyst (bleeding of the ovaries)	Some patients receiving treatment with imatinib may 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 ovaries or womb).	By monitoring early symptoms. The patient should consult the doctor if any of the symptoms occur.
Tumour lysis syndrome (breakdown products of dying cancer cells leading to kidney failure)	Some patients receiving treatment with imatinib may 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).	By monitoring early symptoms. The patient should consult the doctor if any of the symptoms occur.
Growth retardation in children	Some children and adolescents taking imatinib may have slower than normal growth and the growth should be monitored.	By monitoring early symptoms. The patient should consult the doctor if any of the symptoms occur.
Interactions with strong CYP3A4 inhibitors	Concomitant administration of imatinib with drugs such as indinavir, lopinavir/ritonavir, ritonavir, saquinavir,	By monitoring early symptoms. The patient should consult the doctor if

	telaprevir, nelfinavir, boceprevir; azole antifungals including ketoconazole, itraconazole, posaconazole, voriconazole; certain macrolides such as erythromycin, clarithromycin and telithromycin, increase imatinib plasma concentrations, leading to increased chance of occurrence of adverse reactions	any of the symptoms occur.
Interactions with strong CYP3A4 inducers	Concomitant administration of imatinib with drugs such as dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital, fosphenytoin, primidone or Hypericum perforatum, also known as St. John's Wort may significantly reduce exposure to Imatinib, potentially increasing the risk of therapeutic failure.	By monitoring early symptoms. The patient should consult the doctor if any of the symptoms occur.
Interactions with drugs eliminated by CYP3A4	Concomitant administration of imatinib with drugs such as cyclosporine, pimozide, tacrolimus, sirolimus, ergotamine, diergotamine, fentanyl, alfentanil, terfenadine, bortezomib, docetaxel and quinidine, triazolo-benzodiazepines, dihydropyridine calcium channel blockers, certain HMG-CoA reductase inhibitors, i.e. statins, etc.) may influence plasma concentration of either imatinib or the interacting drug, leading to	By monitoring early symptoms. The patient should consult the doctor if any of the symptoms occur.

	increased/decreased effect of the drugs involved.	

Important Potential Risks

Risks with imatinib	What is known
Second Primary malignancies in survivors	During studies on rats, there was an increase in frequency of a second malignancy at doses 2-3 times higher than the human daily exposure. The mechanism and relevance of these findings for humans are not yet clarified.
Disseminated intravascular coagulation (disease characterised by clotting problems, sometimes with bleeding)	There is a lack of conclusive data indicating causal relationship at this time. Should the PV activities uncover additional data, the risk will be communicated through the labelling and additional risk minimisation activities may be proposed if necessary.
Hypoglycaemia (low levels of sugar in the blood)	There is a lack of conclusive data indicating causal relationship at this time. Should the PV activities uncover additional data, the risk will be communicated through the labelling and additional risk minimisation activities may be proposed if necessary.
Suicidality	There is a lack of conclusive data indicating causal relationship at this time. Should the PV activities uncover additional data, the risk will be communicated through the labelling and additional risk minimisation activities may be proposed if necessary.
Tolerability during pregnancy and pregnancy outcomes	There is a lack of conclusive data indicating causal relationship at this time. Should the PV activities uncover additional data, the risk will be communicated through the labelling and additional risk minimisation activities may be proposed if necessary.
Interactions with drugs eliminated by CYP2C9, CYP2C19 and CYP2D6	The prescriber should carefully monitor the early symptoms in patients at risk. The patient should consult the doctor if any of the symptoms occur.

Missing information

Risks with imatinib	What is known
Paediatric patients: long term follow up	Some children and adolescents taking imatinib may have slower than normal growth. The doctor will monitor the growth and other possible effects of treatment at regular visits.
Paediatric patients below 2 years of age	There is no experience with the treatment of children below 2 years of age. It is recommended that the drug should be used with caution when used in children below 2 years of age.
Use in patients with renal impairment	Patients with renal dysfunction or currently undergoing dialysis should be given the minimum recommended dose

Risks with imatinib	What is known
	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.
Use in patients with hepatic impairment	Patients with hepatic impairment should be cautiously monitored and the dose can be reduced if not tolerated.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SPC) 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. 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

This being a generic drug application, no post authorisation development has been planned.

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

The RMP has been updated from version 3 (abbreviated RMP, dated 29-Dec-2012, prepared by Pharos) to version 4 (this document), based on the safety specification of reference product (Glivec) RMP, version 7.0.

The RMP has been updated from version 4 to version 5, in-line with Glivec RMP v 8.0. The safety concerns of interaction with acetaminophen/paracetamol and elderly patients are deleted. In addition to these editorial changes have been made throughout the document.