VI.2 Elements for a Public Summary

Imatinib STADA 100 mg capsules, hard

Imatinib STADA 400 mg capsules, hard

VI.2.1 Overview of disease epidemiology

Imatinib STADA is a medicine containing an active substance called imatinib. This medicine works by inhibiting the growth of abnormal cells in several diseases. These include some types of cancer.

Philadelphia chromosome (bcr-abl) positive (Ph+) chronic myeloid leukaemia (CML)
Leukaemia is a cancer of white blood cells. These white cells usually help the body fight infections. Chronic myeloid leukaemia is a form of leukaemia in which certain abnormal white cells (called “myeloid” cells) start growing out of control. The reason for this excessive multiplication is a chromosomal (genetic) mutation.Each year, 1.6 out of every 100 000 people are newly diagnosed with CML. CML represents 20% of all leukaemias and mainly occurs in adults. Median age at diagnosis is 65 years. Men are slightly more frequently affected than women. Risk factors for the underlying chromosomal mutation include exposure to ionising radiation and certain chemicals.

Philadelphia chromosome positive acute lymphoblastic leukaemia (ALL)
Leukaemia is a cancer of white blood cells. These white cells usually help the body fight infections. Acute lymphoblastic leukaemia is a form of leukaemia in which certain abnormal white cells (called “lymphoblasts”) start growing out of control. The reason for this excessive multiplication is a chromosomal (genetic) mutation. Imatinib STADA inhibits the growth of these cells. Each year, 1.5 out of every 100 000 people are newly diagnosed with ALL. ALL mainly occurs in children (6.5 / 100 000 newly diagnosed cases of ALL occur in children younger than 4 years). ALL is the most common cancer in children, whereas it represents less than 1% of adult cancers. Risk factors for the underlying chromosomal mutation include exposure to ionising radiation and certain chemicals, but often no risk factor can be identified for a specific patient.

Myelodysplastic/myeloproliferative diseases (MDS/MPD)
These are a group of blood diseases in which some blood cells start growing out of control. Imatinib STADA inhibits the growth of these cells in a certain subtype of these diseases. There are three main types of this disease: chronic, juvenile and atypical. The juvenile type is a rare childhood disease and mainly occurs in children younger than 2 years. Risk factors for the chronic type include age, male gender, exposure to ionising radiation or certain chemicals, and past treatment with certain anticancer drugs. The atypical type is another rare disease and most of the people are in their 70s or 80s, when they are diagnosed.

Hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL)
These are blood diseases in which some blood cells (called “eosinophils”) start growing out of control. Imatinib STADA inhibits the growth of these cells in a certain subtype of these diseases. HES and CEL are rare and similar diseases for which the number of newly diagnosed and overall patients cannot be estimated. HES can occur in all age groups, but mostly affects younger to middle-aged people. Men are more often affected.

Dermatofibrosarcoma protuberans (DFSP)

DFSP is a cancer of the tissue beneath the skin in which some cells start growing out of control. Imatinib STADA inhibits the growth of these cells. DFSP is a rare disease and the number of newly diagnosed patients is estimated to be < 5 / million persons per year. DFSP can occur in all age groups, but has mostly been described in patients aged between 30 and 50 years.

VI.2.2 Summary of treatment benefits

Philadelphia chromosome (bcr-abl) positive (Ph+) chronic myeloid leukaemia (CML)
In total, four large international studies were performed in 2 133 adults with the various manifestations of CML, and one study in 54 children. In one study with 1 106 adults, the effect of imatinib was compared to a combination of interferon alpha plus cytarabine. This study demonstrated that patients treated with imatinib lived longer without their cancer getting worse (or: progressing).

Philadelphia chromosome positive acute lymphoblastic leukaemia (ALL)
Treatment benefit could be demonstrated in three clinical studies with 456 adults. In one of those studies, imatinib was compared to standard cancer therapy in 55 newly diagnosed patients. In a fourth study, imatinib was investigated in 120 children and young adults aged between 1 and 22 years. In this study, imatinib successfully prolonged the time without any major event (e.g. cancer coming back).

Myelodysplastic/myeloproliferative diseases (MDS/MPD).
31 patients were studied. Imatinib was not compared with another drug or placebo, but a difference in the number and/or size of cancerous blood cells before and after imatinib administration was evident, demonstrating a treatment benefit.

Hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL)
176 patients were studied. Imatinib was not compared with another drug or placebo, but a difference in the number and/or size of cancerous blood cells before and after imatinib administration was evident, demonstrating a treatment benefit.

Gastrointestinal stromal tumours (GIST)
147 patients with GIST, whose tumour could not be surgically removed or had spread to other organs, were included in the study. Imatinib was not compared to another drug, but measurements showed that the tumour size was successfully reduced. In another study 713 patients, aged 18 to 91 years, were treated with imatinib for adjuvant therapy (after surgical removal of the tumour). It was demonstrated that patients taking imatinib, compared to placebo, clearly lived longer without their cancer coming back.

Dermatofibrosarcoma protuberans (DFSP)
18 patients were studied. Imatinib was not compared with another drug or placebo, but a difference in the number and/or size of cancerous blood cells before and after imatinib administration was evident, demonstrating a treatment benefit.

VI.2.3 Unknowns relating to treatment benefits

<u>Chronic myeloid leukaemia</u>
Except in newly diagnosed chronic phase CML, there are no controlled trials demonstrating that patients taking imatinib live longer or have fewer disease-related complaints.

$\underline{Ph^+ ALL}$
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MDS/MPD, HES/CEL, DFSP
Experience with imatinib in this indication is very limited and is based on the response rate measured by number and/or size of cancerous blood cells. There are no controlled trials demonstrating that patients taking imatinib live longer or have fewer disease-related complaints. There are no controlled trials in paediatric patients with MDS/MPD. Singular scientific observations are available for paediatric patients after imatinib treatment (MDS/MPD: aged 3 months to 4 years, HES/CEL: aged 2 to 16 years).

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Suppressed development and division of bone marrow cells (Myelosuppression)	Given the indication of imatinib to suppress the division of cells developing in the bone marrow, Imatinib STADA can reduce the number of white blood cells. This side effect may affect more than 1 in 10 people. Also, red blood cells might be reduced (up to 1 in 100 people), signs for which are pale skin, feeling tired and breathlessness and having dark urine.	Not specifically. If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in the package leaflet.
Swelling and water retention (Edema and Fluid Retention)	Superficial swellings were a common finding in all studies. Swelling such as around your ankles or puffy eyes may affect more than 1 in 10 people. Joint pain with swelling may affect up to 1 in 10 people, but fluids can also be retained in the lungs and abdominal cavity.	Patients should be weighed regularly. If you experience an unexpected rapid weight gain, tell your doctor.

Bleedings in the brain, stomach or gut (CNS and GI Hemorrhages)	Given the way of action of imatinib to suppress the division of cells developing in the bone marrow, Imatinib STADA may lead to unexpected bleedings (more than 1 in 10 people) and gastrointestinal bleedings and black stools (up to 1 in 100 people). Signs of bleeding or swelling in the skull/brain (up to 1 in 100 people) include severe headache, weakness or paralysis of limbs or face, difficulty speaking, sudden loss of consciousness.	Not specifically. If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in the package leaflet.
Blockage, rupture or inflamed lesion of the digestion tract (Gastrointestinal Obstruction, Perforation or Ulceration)	Severe abdominal pain, blood in your vomit or stools may be signs of gastrointestinal disorders and affect up to 1 in 100 people (ulcer) or 1 in 1000 (obstruction).	Not specifically. If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in the package leaflet.
Harmful effects to the liver (Hepatotoxicity)	Hepatobiliary disorders like increased liver enzymes in the blood (up to 1 in 10), inflammation of liver (up to 1 in 100), or severe liver problems and damage (up to 1 in 1000 people) may occur. Signs of liver problems include feeling sick (nausea), loss of appetite, light-coloured urine and yellow skin or eyes.	Talk to your doctor before taking Imatinib STADA:, if you have or have ever had a liver problem.
Skin Rashes and Severe Cutaneous 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) may affect up to 1 in 100 people.	Not specifically. If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in the package leaflet.

Insufficient activity or availability of thyroid hormones (Hypothyroidism)	Imatinib STADA may decrease the effect of levothyroxine in patients whose thyroid had been removed.	Talk to your doctor before taking Imatinib STADA, if you are taking the medicine levothyroxine because your thyroid has been removed. Your doctor might consider additional blood test during the therapy with Imatinib STADA.
Too low phophorus levels (Hypophosphatemia)	Too low phophorus levels may affect up to 1 in 100 people.	Not specifically. If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in the package leaflet.
Heart failure (Cardiac Failure)	Cardiac failure may affect up to 1 in 100 people. CML status also influences the risk of developing such severe cardiac problems.	Talk to your doctor before taking Imatinib STADA:, if you have or have ever had a heart problem.
Kidney failure (Acute Renal Failure)	Signs of kidney problems include severely decreased urine output and feeling thirsty. Acute renal failure may affect up to 1 in 100 people.	Talk to your doctor before taking Imatinib STADA:, if you have or have ever had a kidney problem.
Severe breathing problems (Severe Respiratory Adverse Reactions)	Cough, having difficulty breathing or painful breathing (signs of lung problems) may affect up to 1 in 100 people. More severe respiratory reactions occure more rarely (up to 1 in 10,000 people).	Not specifically. If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in the package leaflet.
Muscle breakdown and muscle pain (Rhabdomyolysis and Myopathy)	Muscle spasms with a fever, red-brown urine, pain or weakness in your muscles (signs of muscle problems) may affect up to 1 in 1000 people.	Not specifically. If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in the package leaflet.

Bleedings and cysts in the ovaries (Ovarian Hemorrhage and Hemorrhagic 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 your ovaries or womb) may affect up to 1 in 1000 people.	Not specifically. If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in the package leaflet.
Association of several symptoms as a result of destroyed cancer cells (Tumour lysis syndrome)	This syndrome might occur during too rapid breakdown of cancer cells (effect of cancer therapy) and may affect up to 1 in 1000 people. Signs might include 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 phosphorous levels and low calcium levels in the blood).	As prophylaxis, fluid infusions and certain drugs can be administered. Clinically significant dehydration should be treated. Also the posology (amount of drug, dosis interval, dosis escalation steps) can be adapted to lower the risk. Your doctor will take these actions if considered appropriate.
Slowing of growth in children and adolescents (Growth retardation in children)	There have been single case reports of slowed growth in children and adolescents. Frequency of this risk is not known.	Not specifically. If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in the package leaflet.
Interaction with drugs, which inhibit special proteins that are important for eliminating imatinib (Interaction with strong CYP3A4 Inhibitors)	Some medicines can interfere with the effect of Imatinib STADA when taken together. They may increase the effect of Imatinib STADA leading to increased side effects. Some oral antifungals and some antibiotics belong to this group of medicines.	Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription (such as paracetamol).
Interaction with drugs, which activate special proteins that are important for eliminating imatinib (Interaction with strong CYP3A4 Inducers)	Some medicines can interfere with the effect of Imatinib STADA when taken together. They may decrease the effect of Imatinib STADA making Imatinib STADA less effective. Such medicines are e.g. St. John's Wort or dexamethasone.	Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription (such as paracetamol).

Interaction with drugs, which are eliminated by the same proteins than imatinib (Drugs eliminated by CYP3A4)	Imatinib STADA may increase the effect of other medicines (e.g. cholesterol-lowering drugs) leading to increased side effects.	Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription (such as paracetamol).

Important potential risks

Risk	**What is known (Including reason why it is considered a potential risk)**
Second Malignancies in Survivors	Studies in animals have shown carcinogenic effects of imatinib but at doses higher than those administered to humans. The mechanism and relevance of these findings for humans are not yet clarified.
Disseminated Intravascular Coagulation	Patients treated with the medicinal product may be at an increased risk of developing this risk. However, information is too limited and a causal relationship has not been established.
Hypoglycemia	Patients treated with the medicinal product may be at an increased risk of developing this risk. However, information is too limited and a causal relationship has not been established.
Suicidality	Patients treated with the medicinal product may be at an increased risk of developing this risk. However, information is too limited and a causal relationship has not been established.
Tolerability during Pregnancy and Pregnancy Outcomes	There are limited data on the use of imatinib in pregnant women. Studies in animals have however shown harmful effects on the animal foetus and the potential risk for the human foetus is unknown.
Interaction with Drugs Eliminated by CYP2C9, CYP2D6 and CYP3A4/5	Accroding to results obatined in laboratory experiments, an interaction of imatinib with drugs beeing eliminated by the special enzymes CYP2C9 (e.g. warfarin), CYP2D6 (e.g. some antidepressants) or CYP3A4/5 is possible.
Interaction with Paracetamol (Acetaminophen)	Patients treated with the medicinal product may be at an increased risk when using both medicinal products at the same time. However, information is too limited for a sustained warning.

Missing information

Risk	**What is known**

Paediatric patients: 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.
Paediatric patients below 2 years of age	There is no experience in children with CML below 2 years of age. There is limited experience in children with Ph^+ ALL and very limited experience in children with MDS/MPD, DFSP, GIST and HES/CEL.
Renal impairment	Patients with renal dysfunction or on dialysis should be given the minimum dose, as imatinib concentration in the blood may vary in these patients. Data about the underlying mechanism are limited.
Hepatic impairment	As imatinib is mainly eliminated through the liver, patients with mild, moderate or severe liver dysfunction should be given the minimum recommended dose.
Elderly patients	Over 20% of patients included in clinical studies were older than 65 years and no significant differences in drug absorption and elimination have been observed. However, no specific studies have been performed in elderly patients.

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 (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

No post-authorisation studies have been imposed or are planned.

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

Not applicable as this is the first RMP.