## *VI.2 Elements for a public summary*

### VI.2.1 Overview of disease epidemiology

Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder resulting from the neoplastic transformation of the primitive hematopoietic stem cell. The disease is monoclonal in origin, affecting myeloid, monocytic, erythroid, megakaryocytic, B-cell, and, sometimes, T-cell lineages. Bone marrow stromal cells are not involved.

CML accounts for 15% of all leukemias in adults. The age-adjusted incidence is 1.6 per 100,000 population. With imatinib therapy, the annual mortality has been reduced significantly (to less than 2% to 3% per year, with further mortality reductions after the first 2 to 3 years). This has resulted in an increase in prevalence from approximately 70,000 patients in the US in 2010 to a projected 144,000 in 2030.[1]

### *VI.2.2 Summary of treatment benefits*

In the Phase I study, haematologic and cytogenetic responses were observed in all phases of CML and in Ph+ ALL in the first 84 patients treated and followed for up to 27 months. Responses were durable across all phases of CML and Ph+ ALL.

Four single-arm, uncontrolled, open-label Phase II clinical studies were conducted to determine the safety and efficacy of dasatinib in patients with CML in chronic, accelerated, or myeloid blast phase, who were either resistant or intolerant to imatinib. One randomised non-comparative study was conducted in chronic phase patients who failed initial treatment with 400 or 600 mg imatinib. The starting dose was 70 mg dasatinib twice daily. Dose modifications were allowed for improving activity or management of toxicity.

Two randomised, open-label Phase III studies were conducted to evaluate the efficacy of dasatinib administered once daily compared with dasatinib administered twice daily. In addition, one open-label, randomised, comparative Phase III study was conducted in adult patients with newly diagnosed chronic phase CML.
The efficacy of dasatinib is based on haematological and cytogenetic response rates. Durability of response and estimated survival rates provide additional evidence of dasatinib clinical benefit. A total



of 2,712 patients were evaluated in clinical studies; of these 23% were ≥ 65 years of age and 5% were ≥ 75 years of age.

### VI.2.3 Unknowns relating to treatment benefits

The effect of dasatinib on the growth of another cancer discovered either before, during, or after stopping dasatinib is not known as there is no available data from carcinogenicity studies in humans.

No data are available from studies of dasatinib in children under 18 years of age. Therefore, no conclusions can be made about the benefits of dasatinib in children.

There are limited data on the risk of dasatinib in pregnancy and the risk to a baby if a mother on breast feeds during dasatinib treatment. However, due to birth defects and other problems in babies born to mothers who took dasatinib during pregnancy, it is recommended that women taking dasatinib do not become pregnant or breast-feed.

Limited information is currently available for dasatinib use in patients of different racial origins.

## VI.2.4 Summary of safety concerns

**Important identified risks:**

| Risk | What is known | Preventability |
|---|---|---|
| **Low blood counts**<br><br>**(Myelosuppression)** | Treatment with dasatinib causes low red blood cells (anemia), low white blood cells (needed to fight infection), and low platelets (needed for blood clotting).<br><br>Patients with anemia can feel weak or tired. Patients with low white blood cells are at risk of a severe or life-threatening infection. Patients with low platelets are at risk of bleeding.<br><br>The chance of a patient getting low blood counts depends upon whether they have Ph+ ALL or CML. If CML, the chance depends upon the phase of the disease (CP, AP, or BP).<br><br>Patients with Ph+ ALL or advanced CML are more likely to get very low blood counts (as many as 8 out of 10 patients) than patients with CP CML (closer to 4 out of 10). | Your doctor should monitor your blood counts weekly for the first 2 months and then monthly.<br><br>Your doctor will also check your blood counts if there is any other medical reason to do so. This will help your doctor lower your chance of getting seriously low blood counts and complications from low blood counts.<br><br>Tell your doctor immediately if you are very tired, have a temperature, or have bleeding or bleeding that won't stop. |

| Risk | What is known | Preventability |
|---|---|---|
| **Fluid retention** | Dasatinib may cause various types of fluid retention. Fluid around the lining of the lung (pleural effusion) or heart (pericardia! effusion), or fluid in the lungs (pulmonary oedema) may cause shortness of breath. Fluid in the abdomen (ascites) can cause abdominal discomfort or shortness of breath. Fluid under the skin (superficial oedema) can occur in various places in the body and may cause swelling or discomfort.<br><br>Overall, severe fluid retention has been less common now that dasatinib is given once a day. In the study of once a day dasatinib in newly-diagnosed CML patients, fluid retention can occur any time after starting treatment. After a minimum of 4 years of treatment, severe fluid retention was seen in 3% of patients (8/259) and approximately 1 out of 4 patients (62/259) had had a pleural effusion. | Your doctor should monitor you for early symptoms. Most types of fluid retention are easily recognized and managed by your doctor. Fluid retention can usually be managed by stopping dasatinib for a short time or reducing the dose. Sometimes medicine is given (diuretics and/or steroids) to treat pleural effusion or other types of fluid retention.<br><br>If you develop symptoms suggestive of pleural effusion such as shortness of breath or dry cough, call your doctor to arrange for an office visit. Your doctor will likely want to examine you and possibly do other tests such as a chest X-ray. |
| **Bleeding** | Bleeding has been very common in studies with dasatinib affecting more than 1 out of every 10 patients and can occur in any part of the body such as the brain, stomach or intestines. Severe and life-threatening or fatal bleeding has occurred.<br><br>All types of bleeding were more common in the studies in CML and Ph+ ALL where dasatinib was given after imatinib or another therapy (22%) compared to when dasatinib was given as first line treatment with CML (5%). | Most bleeding occurs when patients have very low platelets so checking regular blood counts can lessen the chance of having bleeding.<br><br>Patients need to watch very carefully for signs of bleeding if they also take medicines that inhibit platelet function (like aspirin) or otherwise prevent normal blood clotting (like coumadin). Tell your doctor immediately if you have bleeding or bleeding that won't stop. |

| Risk | What is known | Preventability |
|---|---|---|
| **Changes in the electrical activity of the heart**<br><br>**(QT prolongation)** | Patients on dasatinib can rarely (1% chance or less) have changes in the electrical activity of the heart (QT prolongation). These changes could cause fainting or life-threatening irregular heart rhythms. Heart rhythm changes have been mild and have not caused any serious problems for the patients. | Doctors should be careful when giving dasatinib to patients at risk of getting changes in the electrical activity of the heart. For example, patients who: 1) already have or may develop electrical problems, 2) have too low levels of some minerals in the blood such as calcium, potassium, or magnesium, 3) are taking other medicines that can cause electrical problems.<br><br>If a patient has low levels of minerals, this should be corrected before starting dasatinib. |
| **Birth defects or damage to a fetus in a woman who is taking dasatinib**<br><br>**(Pregnancy-related malformative or foeto/neonatal toxicity)** | Patients treated with dasatinib may be at risk of having a child with birth defects or a pregnancy with a damaged foetus. One seventy-eight pregnancies have been reported in female partners of male patients or female patients on dasatinib. The outcome is not known for all of the pregnancies. In male patients who have female partners who become pregnant, spontaneous abortions and premature delivery of a normal baby have been seen. However, most reported pregnancies end with normal deliveries.<br><br>In female patients on dasatinib, dasatinib is almost always stopped once the woman knows she is pregnant. In 60 of the 104 cases, the diagnosis of pregnancy led to stopping or | Doctors should be careful while giving dasatinib to women of child bearing potential.<br><br>Dasatinib is suspected to cause congenital malformations including neural tube defects, and harmful pharmacological effects on the fetus when administered during pregnancy.<br><br>If you get pregnant while taking dasatinib, tell your doctor immediately. Adverse effects can be prevented by not taking dasatinib while you are pregnant. |

| Risk | What is known | Preventability |
|---|---|---|
| | interruption of patient's dasatinib treatment. In 8 of these cases, women were either switched to (6) or resumed (2) ongoing therapy with interferon or alpha-interferon.<br><br>Birth defects can occur in any pregnancy and spontaneous abortions occur in many pregnancies. It is possible that all the problems with pregnancy and infant and fetal abnormalities reported with dasatinib would have occurred even if the patients were not on dasatinib. However, it is also possible that dasatinib caused the abnormal pregnancies or spontaneous abortions in many or most cases. | |
| **Increase of the pressure within the blood vessels in the lungs**<br><br>**(Pulmonary arterial hypertension)** | Patients treated with dasatinib may be at risk of developing an increase of the pressure within the blood vessels in the lungs, called pulmonary arterial hypertension or PAH. PAH can cause shortness of breath.<br><br>Eighty-six cases of PAH have been reported in patients on dasatinib. Most of the patients were not part of a study so there is limited information on the patients. A special test is needed to prove that a patient has PAH instead of another cause of shortness of breath and that proof was only reported in 39 of these patients. Therefore, the true chance of a patient treated with dasatinib getting PAH is not known. In many cases, PAH gets better or reduces when dasatinib is stopped. | No adequate data are available on potential preventive or mitigating measures for PAH.<br><br>Your doctor will work with you on completing a PAH questionnaire to get detailed information about your diagnosis and treatment of this pre-existing condition.<br><br>Your doctor should monitor you for early symptoms. Sometimes medicine may be given (prostaglandin analogues) to treat your underlying condition. |

| Risk | What is known (Including reason why it is considered a potential risk) |
|---|---|
| **Damage to the liver**<br>**(Severe hepatotoxicities)** | Patients treated with dasatinib may be at increased risk of developing damage to the liver. Other drugs for CML treatment like dasatinib are known to cause liver damage. Patients on dasatinib have had damage to the liver develop. Patients with advanced phase CML or Ph+ ALL are more likely to show evidence of liver damage when on dasatinib. It is unknown if the damage was caused by the treatment or the leukaemia disease itself. |
| **Decreased pumping of the heart**<br>**(Direct cardiotoxic effects)** | Patients treated with dasatinib may be at increased risk of developing heart muscle damage that leads to decreased pumping of the heart and a condition known as Chronic Heart Failure (CHF). CHF can cause shortness of breath. Up to 3% of patients on dasatinib have developed CHF. For example 2.7% (7/259) of previously untreated patients with CP CML developed CHF or decreased pumping of the heart. Most had mild to moderate damage to the heart when they began treatment and several risk factors for heart disease. Therefore, it is not clear if dasatinib caused the decreased pumping of the heart or not. |
| **Potential problems with growth and development in children<18 years of age**<br>**(Growth and development disorders and bone mineral metabolism disorders in paediatric patients)** | Children with leukemia who are receiving standard chemotherapy, radiation therapy or stem cell transplants are at increased risk for growth and development disorders and decreased bone mineralization as a result of their diagnosis and/or treatments. It is unknown if treatment with dasatinib in this setting will alter this risk. Since there is limited data available on the rate of growth and development disorders in children<18 years of age, it is not known if dasatinib therapy has an impact on an individual patient. |
| **Severe skin reactions**<br>**(Toxic skin reactions)** | Based on the currently available information, these happen to be rare events with the use of dasatinib. Impact of the medication may be mild to very severe skin reactions. Patients have been reported to recover once dasatinib was interrupted or stopped. Patients may receive fluids, electrolytes, mechanical supplementation and wound care in some cases for treatment of these skin reactions. |
| **Interactions with other drugs**<br>**(Drug interactions: dasatinib and potent CYP3A4 inhibitors or CYP3A4 substrates)** | Based on the currently available information, not much is known about the occurrence of the meaningful drug interactions with the dasatinib therapy. Attention needs to be given to drugs that are administered along with dasatinib to avoid drugs that may possibly interact with it. Some drugs may increase and some may significantly decrease the effects of dasatinib therapy. All patients should be carefully monitored for dasatinib toxicity. |

**Missing information:**

| Risk | What is known |
|---|---|
| **Another cancer**<br>**(Carcinogenicity)** | Patients in dasatinib studies could not have a recent second cancer so the effect of dasatinib on the growth of another cancer discovered either before, during, or after stopping dasatinib is not known. |
| **Children < 18 years of age**<br>**(Pediatric data)** | No data are available from studies of dasatinib in children. At this time, no conclusions can be made about the benefits of dasatinib in children. |

| | |
|---|---|
| **Pregnancy and breast-feeding**<br><br>**(Reproductive and lactation data)** | There are limited data on the risk of dasatinib in pregnancy and the risk to a baby if a mother on dasatinib breast feeds. However, due to birth defects and other problems in babies born to mothers who took dasatinib during pregnancy, it is recommended that women taking dasatinib do not become pregnant or breast-feed. |
| **Different ethnic or racial populations**<br><br>**(Data in ethnic groups)** | Limited information is currently available for dasatinib use in patients of different racial origins. |

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

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other healthcare 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 (PIL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for dasatinib can be found as Annex 2. 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

Not applicable

## Part VII: Annexes

### *Annex 1 – EudraVigilance Interface*

Not applicable