VI.2 Elements for a Public Summary

VI.2.1. Overview of Disease Epidemiology

Acute lymphocytic leukaemia (ALL) occurs more commonly in children, and, in Europe, ALL is diagnosed in around 3.59 children (ages 0 to 14 years) per 100,000, and in 1.28 out of every 100,000 adults a year. Deaths per 100,000 among children with ALL ages 0 to 14 years occur up to 4 times more often compared to those without ALL.[1] As a result of toxicity from chemotherapy regimens, patients with ALL have an increased chance of heart complications such as myocardial infarction, congestive heart failure, pericardial disease and cardiomyopathy.[2] Other complications from treatment include cerebrovascular and thrombotic events.[3]

In Europe, AML is diagnosed in 3.7 out of every 100,000 adults a year, and in 0.7 among children ages 0 to 14 years, and 0.8 among ages 15 to 24 years.[4] New cases of AML are rising in the population over age 60 years. The diagnosis rate is 9.2 per 100,000 and 10.2 in men and women, aged 65 to 74 years, and even higher among adults aged 75 to 84 years (16.9 and 16.8 in men and women, respectively).[5] Death rates due to AML is higher in adults than in children, ranging from 4 to 6 deaths per 100,000 cases in adults compared to 0.2 in children under 20.[6,7] Patients treated for AML are likely to suffer fatal complications such as multi-organ failure from bacterial and fungal infections.[8,9] Elderly patients with AML are at risk for serious central nervous system toxicities that lead to death.[10]

In Europe, breast cancer is diagnosed in 62.8 women out of every 100,000 each year, and among new cases, 20% to 25% have locally advanced breast cancer.[11,12] Among every 100,000 women who are diagnosed with breast cancer in the EU, approximately 22.4 will die each year.[13] Women who are diagnosed with breast cancer at an advanced age may be more likely than younger women to die of breast cancer. Breast cancer patients are more likely to have other medical conditions such as hypertension, heart conditions, stroke, emphysema/ asthma/chronic obstructive pulmonary disease, Crohn's Disease, arthritis of the hip, and diabetes.[14]

VI.2.2. Summary of Treatment Benefits

Idarubicin is a cancer drug (chemotherapy drug) belonging to a drug class called anthracyclines. Idarubicin works by killing rapidly dividing cells and interferes with ways in which the cells of human body grow and increase in number, such as cancer cells.

Four prospective randomized studies have been conducted to evaluate the efficacy and safety of idarubicin in untreated adult patients with AML.

Study (Country))/ Number of evaluable participants (N)	Survival and Remission Results
MSKCC[15] (US)/ N = 120	Complete remission (CR) was observed in 48 of 60 patients (80%) receiving IDA/Ara-C compared to 35 of 60 patients (58%) receiving DNR/Ara-C. Overall survival for patients on the IDA/Ara-C arm was 19.7 months compared with 13.5 months in patients on the DNR/Ara-C.

SEG[16] (US)/ N = 218	The CR rates were 71% (75 of 105) on the IDA arm compared with 58% (65 of 113) on the DNR arm. The median survival and median duration of remission were 297 and 433 days, respectively in the IDA arm, and 277 and 328 days, respectively in the DNR arm.
US multicentre trial[17]/ N = 208	The CR rates were 70% (68 of 97) in IDA arm compared with 59% (65 of 111) in DNR arm. The median duration of response was 9.4 months in IDA arm (n = 68) and 8.4 months in DNR arm (n = 66). The median survival for the IDA and DNR groups was 12.9 months and 8.7 months, respectively.
GIMEMA[18] (Italian) / N = 257	Of the 131 patients who received IDA alone as induction treatment, 100 (76.3%) achieved CR, 11 (8.4%) were resistant and 20 (15.3%) died during induction. Of the 126 patients who received IDA + Ara C, 84 (66.6%) had CR, 15 (11.9%) were resistant and 27 (21.4%) died. Event-free survival (EFS) rates were 35% and 23% for patients in IDA group and IDA + Ara C group, respectively. Improved CR and EFS rate in IDA group versus IDA + Ara C group.

IDA = idarubicin; Ara-C = cytarabine; DNR = daunorubicin; CR = completed remission; EFS = event free survival

VI.2.3. Unknowns Relating to Treatment Benefits

No major differences in treatment benefit with idarubicin were seen across age, gender or ethnicity. Investigators continue to actively study the drug in a controlled clinical setting in different protocols in order to optimize its therapeutic benefit for its approved indications.

VI.2.4. Summary of Safety Concerns

Table 1. Important Identified Risks

Risk	What is Known	Preventability
Heart rhythm changes which may include irregular, slow or rapid heartbeat. (Acute cardiotoxicity)	Common side effects in patients receiving idarubicin (may affect up to 1 in 10 people) may include an increase or decrease in heart rate, or irregular heart beat/pulse. An uncommon side effect (may affect up to 1 in 100 people) may include ECG changes.	Physician supervision and care. Before starting and during treatment you will need regular checks including heart tests.
Heart muscle disease (Cardiomyopathy)	Congestive heart failure is the most severe form of cardiomyopathy caused by idarubicin and sometimes limits how many treatments patients can receive. Common side effects in patients receiving idarubicin (may affect up to 1 in 10 people) may include heart failure.	Physician supervision and care. Before starting, during and after treatment you will need regular checks including heart tests.
Abnormally low number of white blood cells, red blood cells or platelets in the bloodstream (Myelosuppression and increased susceptibility to infections)	A decrease in the number of red blood cells, white blood cells or abnormally low amount of platelets may affect more than 1 in 10 patients receiving idarubicin (very common). A decrease in the number of white blood cells can make someone more susceptible to infections.	Physician supervision and care. Before starting and during treatment you will need regular checks including blood tests.
Cancer of the blood	Though used to treat cancer, idarubicin can	Physician supervision and

Table 1. Important Identified Risks

Risk	What is Known	Preventability
caused by medication to treat cancer (Secondary leukaemia)	sometimes cause new cancers, including cancers of blood such as leukaemia or myelodysplastic syndrome (MDS). These may occur many years after treatment and may affect up to 1 in 100 patients (uncommon).	care.
Irritation to the lining of the mouth, oesophagus, stomach and intestines, which if severe enough can result in perforation (puncture to the lining) (Mucositis/stomatitis/ esophagitis)	Feeling sick, pain in the mouth and/or throat, diarrhoea, stomach ache and similar symptoms may affect more than 1 in 10 patients receiving idarubicin (very common). Inflammation of the oesophagus or colon may affect up to 1 in 100 patients receiving idarubicin (uncommon). Symptoms generally appear early after drug administration and usually resolve by the third week of therapy. Occasionally, episodes of serious gastrointestinal events (perforation or bleeding) have been observed in patients receiving oral idarubicin.	Physician supervision and care. There are no known specific preventive measures to reduce the risk of mucositis, stomatitis and oesophagitis in patients treated with idarubicin.
A serious condition when cancer treatment causes cancer cells to die quickly (Tumour lysis syndrome)	Tumour lysis syndrome can occur when the dying cancer cells break down and release material into the bloodstream, resulting in damage to the kidneys. Symptoms include nausea, shortness of breath, irregular heartbeat, muscular cramps, seizures (convulsions), clouding of urine and decreased amount of urine and tiredness (frequency cannot be estimated from the available data). Frequency cannot be estimated from the available data.	Physician supervision and care.

Table 2. Important Potential Risks

Risk	What is Known	Preventability
May experience more and/or severe toxic reactions if your liver does not work properly (Increased toxicity in patients with hepatic impairment)	Idarubicin has not been fully evaluated in patients who have liver problems. The dose may need to be decreased in patients with mild liver problems. Idarubicin should not be used in patients with severe liver disease. Frequency cannot be estimated from the available data.	Physician supervision and care. Regular medical examinations and periodic blood tests to check liver function.
May experience more and/or severe toxic reactions if your kidneys do not work properly (Increased toxicity in patients with renal impairment)	Idarubicin has not been fully evaluated in patients who have kidney problems. The dose may need to be decreased in patients with mild kidney problems. Idarubicin should not be used in patients with severe kidney disease. Frequency cannot be estimated from the available	Physician supervision and care. Regular medical examinations and periodic blood tests to check kidney function.

Table 2. Important Potential Risks

Risk	What is Known	Preventability
	data.	

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 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

There are no post-authorisation studies planned.

VI.2.7. Studies that are a Condition of the Marketing Authorisation

There are no studies that are conditions of the Marketing Authorisation.

VI.2.8. Summary of Changes to the Risk Management Plan Over Time

Major changes to the Risk Management Plan over time are shown in **Table 3**

Table 3. Major Changes to the Risk Management Plan Over Time

Version	Date	Safety Concerns	Comment
1.0	22 May 2015	Initial RMP	-
1.1	17 March 2016	1) Missing information deleted 2) Important potential risks added 3) Pivotal trial information added to Summary of Treatment Benefits 4) Footnote added for Indications in the Product Overview regarding advanced breast cancer	This update is in response to WS procedure DE/H/xxxx/WS/281 Day 55

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