VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Acute non-lymphocytic leukemia in adults (ANLL):

Acute non-lymphocytic leukemia is one type of blood cancer, commonly called as acute myeloid leukemia (AML). The incidence of acute myeloid leukemia in adults in Europe is 5–8 cases/100,000/year. The death rate is approx 4–6 cases/100 000/year. [(2)] Acute myeloid leukemia (AML) accounts for approximately 25% of all leukemias in adults in the Western world, and therefore is the most frequent form of leukemia. Worldwide, the incidence of AML is highest in the U.S., Australia, and Western Europe. AML is primarily a disease of later adulthood. The distribution of the proportion of prevalent cases of all leukemias in the U.K. shows that 42.8% of patients are age >65 years. Patients newly diagnosed with AML have a median age of 65 years. [(3)]AML in adults has a slight male predominance in most countries. The development of AML has been associated with several risk factors. These include age, blood disorders, exposures to viruses as well as radiation, chemical, or other harmful substances and treatment with chemotherapy (drugs used to treat other cancers) and weakened immune system due to organ transplant [(2)]

Acute lymphocytic leukemia in adults and children (ALL):

Acute lymphoblastic leukemia is a fast-growing cancer of a type of white blood cells called lymphoblast. ALL is uncommon in adults. About 10,000 new cases are diagnosed in adults in Europe each year. In adults, ALL represents about 15% of leukemias: the chronic form is five times more common. ALL affects white more than blacks, males more than females, and those in Western, affluent countries more than those in the developing countries. The annual incidence

rates in Europe were 1.3 per 100,000 in men and 0.9 in women. In adults aged 15 and over, half the cases is under age 50, and ALL is rare over the age of 70. ALL is the most common malignancy in children, accounting for 30% of all cancers and 80% of all leukemias. In children almost two-thirds of the cases occur in age from 2 to 6 years. Common risk factors for ALL include genetic disorders exposures radiation including X-rays before birth, or other toxic substances like benzene and past treatment with chemotherapy drugs. (4)

VI.2.2 Summary of treatment benefits

Acute non-lymphocytic leukaemia in adults:

Chemotherapy is the main treatment for most people with this cancer. Treatment is usually divided into two phases. Induction is the first phase of treatment and the goal is to clear the cancer cells (blasts) and to reduce the number of blasts in the bone marrow to normal. Consolidation phase comes after induction and it is meant to kill the small number of cancer cells that are still around but can't be seen. The chemotherapy drugs used most often to treat AML are cytarabine (cytosine arabinoside or ara-C) and the anthracycline drugs (such as daunorubicin, idarubicin, and mitoxantrone). Idarubicin can be a choice of drug to induce remission as first-line treatment or to induce remission in relapsed or resistant patients. Patient's not entering complete remission after induction therapy should be considered candidates for allogeneic transplantation (the patient receives bone marrow from another person, usually a sibling or unrelated donor). (2)

Acute lymphocytic leukaemia as second-line treatment in adults and children:

Treatment recommendations for patients who are diagnosed with ALL include induction, consolidation and maintenance therapy along with CNS prophylaxis. Patients receive induction therapy with combinations of drugs, including vincristine, prednisone, cyclophosphamide, doxorubicin, and L-asparaginase. Consolidation therapy with multiagent, including cytarabine and methotrexate is effective. Maintenance therapy includes 6-mercaptopurine, methotrexate, steroids, and vincristine. (5) Idarubicin is generally recommended as second-line treatment in adults and children suffering from ALL. Idarubicin is a very effective drug for the early management of adult acute lymphoblastic leukaemia and may be presently considered (along

with cyclosporin-A or other modulator) as the reference anthracycline for cases over expressing the P-glycoprotein drug resistance mechanism.[6]

VI.2.3 Unknowns relating to treatment benefits

The efficacy and safety of idarubicin has not been established in pregnant and lactating women.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Cardiotoxicity (including arrhythmias, cardiomyopathy, congestive heart failure) {Damage to the heart (including an abnormal heart rhythm caused by a disruption of the electrical signals that control the heartbeat, a weakening of the heart muscle, heart problem that causes shortness of breath and the body to swell, or hold water)	These are common side effects with idarubicin which may affect up to 1 in 10 people. Very high doses of Idarubicin can cause acute toxicity of the heart muscle (myocardium) in the first 24 hours and severe suppression of blood cell production through the marrow (myelosuppression) within one to two weeks. The occurrence of delayed heart failure with anthracyclines has been observed, up to several months after an overdose. The risk of cardiac toxicity (damage to the heart) may increase in patients who have	Yes Do not use Idarubicin Accord • If you have heart problems Talk to your doctor before using Idarubicin Accord • If you have heart function impairment. Heart function must be assessed before starting treatment with idarubicin and must be monitored during treatment to minimise the risk of incurring severe heart failure • Tell your doctor if you are taking or have recently taken, or if you will be taking other medicines

	received at the same time other medicines which can have toxic effect on heart.	with Idarubicin Accord
Haematological toxicity (damage to the blood and blood forming tissues) including - low numbers of white blood cells in the blood that fight infection [leucopenia], low numbers of a type of white blood cells called neutrophils that fights infections and are part of white blood cells [neutropenia], low number of platelets in the blood which are the part of the blood that helps stop bleeding [thrombocytopenia]. the breakdown of red blood cells, the part of the blood that carries oxygen to the rest of the body [anaemia]	These are very common side effects which may affect more than 1 in 10 people. Very high doses of Idarubicin can cause suppression of blood cell production through the marrow (myelosuppression) within one to two weeks. Idarubicin is used mainly in association with other medicines for treating cancer (cytotoxic agents), and an increase in toxicity may occur, especially with regard to bone marrow and blood. Dosage patterns must take into account the patient's blood condition and the doses of the other cytotoxic agents when used in association. Accord Idarubicin is contraindicated in patients with persistent myelosuppression (fewer red and white blood cells and platelets made in the	Yes Do not use Idarubicin Accord • If you have reduced blood cell and platelet production Talk to your doctor before using Idarubicin Accord • If you have a reduced bone marrow blood cell and platelet count • If you have a marked and permanent increase of abnormal white cells in the blood. You may be developing leukaemia • As happens with other cancer treatment medicines (cytotoxic agents), inflammation of a vein wall may occur, with the formation of blood clots • Tell your doctor if you

	bone marrow) Very high doses of idarubicin may cause severe myelosuppression (fewer red and white blood cells and platelets made in the bone marrow) within one to two weeks	are taking or have recently taken, or if you will be taking other medicines. • Before starting treatment with idarubicin, the patient must recover from severe toxicity (such as neutropenia, thrombocytopenia and general infections) of previous cytotoxic treatments.
Secondary leukemia (development of new blood cancer in patients with previous history of cancer)	This is uncommon side effect which may affect up to 1 in 100 people. Idarubicin is used mainly in association with other medicines for treating cancer (cytotoxic agents), and an increase in toxicity may occur, especially with regard to bone marrow, blood. Dosage patterns must take into account the patient's blood condition and the doses of the other cytotoxic agents when used in association.	Yes Talk to your doctor before using Idarubicin Accord • If you have a marked and permanent increase of abnormal white cells in the blood. You may be developing leukaemia.

Gastrointestinal toxicity (including mucositis, perforation, hemorrhage) (damage to the Stomach and intestines (including inflammation of lining of mouth, food pipe, stomach and intestine, puncture, tear or hole, severe bleeding)	Inflammation of mucosa in the mouth is a very common side effect which may affect more than 1 in 10 people. Pain in stomach and bleeding are common side effects which may affect up to 1 in 10 people Inflammations of the oesophagus, inflammation of the colon are uncommon side effect which may affect up to 1 in 100 people. Stomach ulcer is very rare side effect which may affect up to 1 in 10,000 people. Idarubicin is used mainly in association with other medicines for treating cancer (cytotoxic agents), and an increase in toxicity may occur, especially with regard to bone marrow, blood and stomach/intestine.	Yes Talk to your doctor before using Idarubicin Accord • If you have gastrointestinal problems • Idarubicin must only be administered under the supervision of doctors with experience in cytotoxic chemotherapy. Thus, it will be possible to treat quickly and effectively severe complications of the disease and/or of the treatment {for example, haemorrhage (severe bleeding), and severe infections)}. • Before starting treatment with idarubicin, the patient must recover from severe toxicity (such as mouth sores) of previous cytotoxic treatments.
Extravasation (blood leaking outside of a blood vessel-	The ready-to-use solution of Idarubicin Accord must only be	Yes Talk to your doctor before

vein)	administered through vein. Also flushing of solution (sodium chloride) should be done for a period of 5 to 10 minutes after idarubicin administration. This method minimizes the risks of thrombosis or perivenous extravasation that can lead to severe cellulitis (pain, redness, swelling of the surrounding skin) and necrosis (death of surrounding skin and tissue).	using Idarubicin Accord • If extravasation occurs during the injection, you may feel pain and extravasation may cause severe tissue lesions. • If extravasation occurs, administration of the medicine must be stopped immediately.
Severe infections	This is very common side effect which affects more than 1 in 10 people. Administration of live vaccines can result in severe or fatal infections. Due to weakened immune system, chances of getting infection increase.	Yes Talk to your doctor before using Idarubicin Accord, If you have recently had or thinking of having a vaccine Vaccinating patients on treatment with idarubicin with live vaccines should be avoided. Vaccines of dead or inactivated organisms can be administered. However, the response to the vaccination may be reduced. Before starting treatment with idarubicin, the patients must recover from general

		infections of previous cytotoxic treatments.
Tumour lysis syndrome (serious condition including imbalance in minerals and other chemicals of the body and kidney failure, that can happen when cancer treatment causes cancer cells to die quickly)	Cases of tumour lysis syndrome have been reported. Increase in blood uric acid concentration is an uncommon side effect which may affect up to 1 in 100 people. Idarubicin may induce hyperuricaemia (too much of the chemical called uric acid in the blood) as a result of extensive purine catabolism (breakdown), which goes together with the breakdown of cancer cells When the patient stop treatment with Idarubicin Accord, the effect on tumour growth may stop.	Yes The serum levels of uric acid, potassium, calcium phosphate and creatinine must be assessed after the initial treatment.
Irreversible infertility (problems having children) in males	Idarubicin can induce chromosome (structures that hold the genes) impairments in human sperms.	Yes Male patients should talk to their doctor before using Idarubicin Accord Male patients treated with idarubicin hydrochloride are advised to take effective contraceptive measures

		during treatment and, if appropriate and available, to seek advice on how to store sperm, due to the possibility of irreversible infertility caused by the treatment occurring.

Important potential risks

Risk	**What is known**
Drug exposure in pregnancy	The embryotoxic (toxic effects on foetus) potential of idarubicin has been shown in studies in vitro (In a test tube) and in vivo (In the body). However, there are no appropriate controlled studies in pregnant women. Women of child-bearing age must be advised to avoid becoming pregnant and must use effective contraceptive measures during treatment. Idarubicin should only be used during pregnancy if the potential benefits justify the potential risks for the foetus. The patient must be informed of the potential harmful effects for the foetus. Female patients who wish to have children after the end of the treatment must be recommended to obtain genetic advice, if appropriate and available. Pregnant women must be excluded from working with this drug

Missing information

Risk	What is known
Drug exposure via lactation	It is not known whether idarubicin or its metabolites are excreted in the mother's milk. Breast-feeding women should stop breast-feeding during treatment with idarubicin hydrochloride.

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 minimization measures.

VI.2.6 Planned post authorisation development plan

No studies planned.

VI.2.7 Summary of changes to the risk management plan over time

Version	Date	Safety Concern	Comment
2.0	20-Jul-2015	Following safety concerns are removed: **Missing information**: ➢ Pregnancy and lactation Following safety concerns are added:	As per comment received from Portugal regulatory authority: safety concerns have been updated, with updation in relevant sections of risk

Version	Date	Safety Concern	Comment
		Important Identified risks ➢ Cardiotoxicity (including arrhythmias, cardiomyopathy and congestive heart failure) ➢ Haematological toxicity (including leucopoenia, neutropenia, thrombocytopaenia and anaemia) ➢ Secondary leukemia ➢ Gastrointestinal toxicity (including mucositis, perforation and hemorrhage) ➢ Extravasation ➢ Severe infections ➢ Tumour lysis syndrome ➢ Irreversible infertility in males **Important potential risks** ➢ Drug exposure during pregnancy **Missing information**	management plan.

Version	Date	Safety Concern	Comment
		➢ Drug exposure via lactation	