VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Acute Lymphoblastic Leukemia

Acute lymphoblastic leukemia (ALL) is a form of cancer that arises from cells of the immune system, which are called lymphocytes. There are two main types of lymphocytes: B cells and T cells. The B cells produce antibodies that are used to attack invading bacteria, viruses, and toxins. The T cells destroy the body's own cells that have themselves been taken over by viruses or become cancerous [9]. In ALL, malignant immature lymphocytes in the bone marrow increase in number in an uncontrolled way. Lymphocytes are mainly localized in the bone marrow, the blood, bone lymph nodes and the spleen. The disease develops in a couple of weeks and leads to a change in the normal way that remaining blood cells are produced, causing hemorrhages, anemia and susceptibility for infection.

Acute lymphoblastic leukemias are predominantly cancers of children and young adults. Childhood ALL occurs more often in higher socioeconomic subgroups. The relative frequency of ALL compared to other lymphoid cancers is 3.8% [9]. The incidence rate of ALL during 2003-2007 ranged from 1.08-2.12 per 100,000 person-years based on information worldwide. Risk factors for acute lymphoblastic leukemia are previous cancer treatment, exposure to radiation, genetic disorders and sibling with acute lymphoblastic leukemia.

Acute Myeloblastic Leukemia

Acute myeloblastic leukemia (AML) is a form of cancer characterized by presence of abnormal undifferentiated myeloid cells in the blood, bone marrow, and other tissues [9]. These abnormal myeloid cells are primarily granulocytes (which destroy bacteria) or monocytes (which produce large cells called macrophages, which digest foreign substances and diseased cells) [18]. These leukemias comprise a spectrum of cancers that, if untreated, range from slowly growing to rapidly fatal. In 2013, the estimated number of new AML cases in the United States was 14,590. The incidence of AML is ~3.5 per 100,000 people per year, and the age-adjusted incidence is higher in men than in women (4.5 vs 3.1). AML incidence increases with age; it is 1.7 in individuals age <65 years and 15.9 in those age >65 years. The median age at diagnosis is 67 years [9].

VI.2.2 Summary of treatment benefits

The standard of treatment includes combination chemotherapy. Young patients can be candidates for bone marrow transplantation. Bone marrow transplantation can be curative but is associated with a significant treatment-related death rate [9]. Amsacrine is a kind of chemotherapy and it is administered through in the veins. It blocks the production of DNA, which is the hereditary material found in cells. Blockage of DNA production will lead to reduction of cancer cells.

VI.2.3 Unknowns relating to treatment benefits

There is not enough information on the effects of amsacrine exposure during pregnancy or on the excretion in breastmilk. However, based on the pharmaceutical class and pharmacokinetic action of amsacrine, amsacrine must not be used when a patient is breastfeeding.

VI.2.4 Summary of safety concerns

Summary of safety concerns – important identified risks

Risk	**What is known**	**Preventability**
Damage to the blood cells and decreased functioning of bone-marrow (Hematologic toxicity and bone-marrow suppression)	Amsacrine can cause severe bone-marrow suppression because Amsacrine inhibits the cell division. Abnormalities in blood cells can be rare to common (frequency ranging from (≥1/10.000 to <1/1000 to (≥ 1/100 to <1/10).	Extra blood tests should be performed because amsacrine can cause severe bone-marrow-depression.
High susceptibility to infections	This is the most common adverse event related to Amsacrine, based on the results of clinical studies. The frequency of occurrence is ≥ 1/100 to <1/10. The risk of infections depends on the intensity of the treatment with Amsacrine. Because the activity of the bone marrow is decreased, especially the development of white blood cells which play a role fighting against infections, the risk of infection is higher in patients on Amsacrine treatment.	Extra blood controls may be performed monitor the amount of white blood cells in the patient's blood.
Adverse drug reaction on the stomach and intestines (Gastro-intestinal adverse drug reactions)	Bleeding from the stomach and intestines is a common side effect, with a frequency of ≥ 1/100 to <1/10. The lining of the stomach and intestines is sensitive to adverse reactions because the cells in this layer multiply fast. This is affected because Amsacrin inhibits cell division.	Increase awareness of the risk prior to administration of Amsacrine
Allergic reactions to Amsacrine (Hypersensitivity / allergic reactions)	Allergic reactions associated with Amsacrine treatment are very rare, with a frequency of (≥1/10.000 to <1/1000. Clinical trials show an approximated incidence of hypersensitivity to Amsacrine of 0.4%. Life-threatening systemic allergic reactions are very rare, but they can occur.	Hypersensitivity to Amsacrine is mentioned as a contraindication in section 4.3 of the SmPC.
Damage to the heart (Cardiac toxicity)	Damage to the heart is known to commonly occur in patient on Amsacrine treatment	Hypokalemia should be corrected prior to administration of Amsacrin.

	(frequency of (≥ 1/100 to <1/10). Studies including more than 6,000 patients who have received Amsacrine showed that cardiac toxicity occurred in just above 1% of the patients.[12]	
Leakage of the drug out of the veins (Cytostatic extravasation)	Infrequently, Amsacrine is reported to cause local cell death of tissue when it leaks out of the vein into which it was administrated. When there is access to a vein for the administration of Amsacrine.. Injection site irritation and damage to the nearby tissues are known to commonly occur, with a frequency of ≥ 1/100 to <1/10.	In case Amsacrine leaks out of the vessel, it is recommended to rinse with a small amount of glucose solution 50 mg/L after which the body part should immediately be cooled down. The infusion shall be stopped and started in a different vessel.

Summary of safety concerns – important potential risks

Risk	**What is known**
Medication error	Medication which inhibits cell growth and cell division (cytostatics) should be handled in accordance with national requirements. Any unused medicinal product or waste material should be disposed in accordance with local requirements. A dilution failure or an incorrect solution for dissolving the powder could pose a risk of administration of an incorrect dose. The SmPC contains clear guidance on the method of administration and includes recommendations to prevent inflammation of veins, known as phlebitis.
Interaction with drugs	When an influenza or pneumococcal vaccination is administered at the same time with Amsacrine, this has been linked to the possibility that the body will not respond well to the administered vaccine.. In general, concomitant administration of all types of live vaccines are a potential risk.
Breast feeding (Lactation)	It is unknown whether Amsacrine is excreted via breast milk. Breast-feeding is contraindicated with the use of Amsacrine
Pregnancy	Data from the use of Amsacrine in pregnant women are not available to judge possible harm to the unborn foetus. However, harmful pharmacological effects during pregnancy are possible. Based on animal studies and the mechanism of action of the substance, use during pregnancy is discouraged, especially during the first trimester. In every individual case, the advantages of treatment should be weighed against the risks to the foetus.
Use in children (Pediatric population)	Amsacrine is not authorised for use in the paediatric population. No relevant information regarding the effect of age on the pharmacokinetics or tolerability of amsacrine is available
Overdosing	No specific antidote is known in case of overdosage. Treatment should be intended to treat the symptoms and support the bodily functions.

Risk	What is known
	Bleeding (haemorrhage) and infection, resulting from reduced blood cell production in the bone marrow, may require intensive treatment with red blood cell, white blood cell or platelet transfusions and appropriate antibiotics to support the bodily functions. Even stronger symptomatic treatment may be necessary for severe inflammation of the lining of body organs, vomiting or diarrhea.
Disorders in the reproductive system (including ovaries, testes), congenital, hereditary and genetic disorders in patients who can produce children	Due to the mechanism of action of amsacrine and possible adverse effects on the foetus, women of child-bearing potential have to use effective contraception during and up to 3 months after treatment and also males during and up to 6 months after treatment. There have been reports of low sperm count in males, although this effect is reversible. Although there is no evidence, some reports suggest that amsacrine can affect fertility in females.
Patients with impaired liver and/or impaired kidney function	Caution is advised when administering amsacrine to patients with kidney impairment. In patients with mild impaired functioning of the kidneys, no starting dose adjustment is recommended. In patients with moderate or severe kidney impairment, a starting dose reduction by approximately 20-30% should be considered. Subsequent dose adjustments may be needed based on how much damage is seen in patients after administration of amsacrine. Caution is advised when administering amsacrine to patients with liver impairment. In patients with mild liver impairment, no dose adjustment is necessary and they should be able to tolerate the full dose. In patients with moderate or severe liver impairment, a starting dose reduction of approximately 20-30% should be considered. Subsequent dose adjustments may be needed based on how much damage is seen in patients after administration of amsacrine.

Summary of safety concerns –Missing information

Risk	What is known
Elderly	No relevant information is available regarding the effect of age on the processing of amsacrine in the body, or tolerability of amsacrine.
Build up of porphyrins, which are proteins found in red blood cells (Porphyria)	It has been suggested that Amsacrine can cause porphyria

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

No post-authorisation studies are planned and therefore this section is not applicable.

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

Not applicable, since this is the first RMP of Amsacrine.