Part VI: Summary of the risk management plan by product

VI.1 Elements for summary tables in the EPAR

VI.1.1 Summary table of Safety concerns

Summary of safety concerns	
Important identified risks	Hematologic toxicity and bone-marrow suppression
	High susceptibility to infections
	Gastro-intestinal adverse drug reactions
	Hypersensitivity/ allergic reactions
	Cardiac toxicity

Summary of safety concerns	
	Cytostatic extravasation
Important potential risks	Medication error
	Interactions with other drugs
	Lactation
	Pregnancy
	Paediatric population
	Overdosing
	Reproductive system, congenital, familial and genetic disorders in patients in the reproductive age
	Patients with impaired liver and/or impaired renal function
Missing information	Elderly
	Porphyria

VI.1.2 Table of on-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan

There are no on-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan.

VI.1.3 Summary of Post authorisation efficacy development plan

There is no Post authorisation efficacy development plan

VI.1.4 Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Hematologic toxicity and bone-marrow suppression.	Proposed text in SmPC and PIL and routine PhV activities. Other routine risk minimisation measures: - Prescription only medicine Use restricted to physicians experienced in the treatment of acute leukaemia.	None proposed
High suceptibility to infections	Proposed text in SmPC and PIL and routine PhV activities. Other routine risk minimisation measures: - Prescription only medicine Use restricted to physicians experienced in the treatment of acute leukaemia.	None proposed
Gastro-intestinal adverse drug reactions	Proposed text in SmPC and PIL and routine PhV activities. Other routine risk minimisation	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	measures: - Prescription only medicine Use restricted to physicians experienced in the treatment of acute leukaemia.	
Hypersensitivity/ allergic reaction	Proposed text in SmPC and PIL and routine PhV activities. Other routine risk minimisation measures: - Prescription only medicine Use restricted to physicians experienced in the treatment of acute leukaemia.	None proposed
Cardiac toxicity	Proposed text in SmPC and PIL and routine PhV activities. Other routine risk minimisation measures: - Prescription only medicine Use restricted to physicians experienced in the treatment of acute leukaemia.	None proposed
Cytostatic extravasation	Proposed text in SmPC and PIL and routine PhV activities. Other routine risk minimisation measures: - Prescription only medicine Use restricted to physicians experienced in the treatment of acute leukaemia.	None proposed
Medication error	Proposed text in SmPC and PIL and routine PhV activities. Other routine risk minimisation measures: - Prescription only medicine Use restricted to physicians experienced in the treatment of acute leukaemia.	None proposed
Interactions with other drugs	Proposed text in SmPC and PIL and routine PhV activities. Other routine risk minimisation measures: - Prescription only medicine Use restricted to physicians experienced in the treatment of acute leukaemia.	None proposed
Lactation	Proposed text in SmPC and PIL	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	and routine PhV activities. Other routine risk minimisation measures: - Prescription only medicine Use restricted to physicians experienced in the treatment of acute leukaemia.	
Pregnancy	Proposed text in SmPC and PIL and routine PhV activities. Other routine risk minimisation measures: - Prescription only medicine Use restricted to physicians experienced in the treatment of acute leukaemia.	None proposed
Pediatric Population	Proposed text in SmPC and PIL and routine PhV activities. Other routine risk minimisation measures: - Prescription only medicine Use restricted to physicians experienced in the treatment of acute leukaemia.	None proposed
Overdosing	Proposed text in SmPC and PIL and routine PhV activities. Other routine risk minimisation measures: - Prescription only medicine Use restricted to physicians experienced in the treatment of acute leukaemia.	None proposed
Reproductive system, congenital, familial and genetic disorders in patients in the reproductive age	Proposed text in SmPC and PIL and routine PhV activities. Other routine risk minimisation measures: - Prescription only medicine Use restricted to physicians experienced in the treatment of acute leukaemia.	None proposed
Patients with impaired liver and/or impaired renal function	Proposed text in SmPC and PIL and routine PhV activities. Other routine risk minimisation measures: - Prescription only medicine Use restricted to physicians experienced in the treatment of	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	acute leukaemia.	
Elderly	Proposed text in SmPC and PIL and routine PhV activities. Other routine risk minimisation measures: - Prescription only medicine Use restricted to physicians experienced in the treatment of acute leukaemia.	None proposed
Porphyria	Proposed text in SmPC and PIL and routine PhV activities. Other routine risk minimisation measures: - Prescription only medicine Use restricted to physicians experienced in the treatment of acute leukaemia.	None proposed

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Acute leukaemia (acute blood cancer) occurs in the bone marrow precursors of blood cells. There are two types of acute leukaemia: acute myeloid leukaemia (AML) and acute lymphocytic leukaemia (ALL). Acute leukaemia may lead to fatal infection, bleeding or organ infiltration, typically in the absence of treatment, within 1 year of diagnosis. Without treatment, most patients would live only a few months.

The cause is often unknown however exposure to radiation, certain chemicals and certain types of chemotherapy increases the risk of acute leukaemia.

AML is the most common form among adults. The yearly number of newly identified patients with AML in European adults is 5-8 cases per 100,000 individuals. In individuals >60 years the incidence increases significantly and rises to 18 per 100,000 adults aged >65 year. ALL is the most common type of leukaemia among children, but it is actually the least common type among adults.

VI.2.2 Summary of treatment benefits

When treated with m-AMSA patients suffering from acute leukaemia experience increased survival time and the disease free period increases.

VI.2.3 Unknowns relating to treatment benefits

Elderly and patients with pre-existing medical conditions such as diabetes, coronary heart disease or chronic obstructive pulmonary disease (COPD) are more susceptible to treatment complications than younger patients and are less likely to be able to tolerate intensive therapy than younger patients, so generally their disease does not respond as well to treatment.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Hematologic toxicity and bone-marrow suppression	Myelosuppression (bone marrow suppression) is dose-limiting and the most important consequence of m-AMSA therapy. The degree of myelosuppression is dose dependent and is reversible. Myelosuppression increases the risk of bleeding and infections.	Hematologic toxicity is prevented by closely monitoring the blood picture of the patient before and during treatment. In the SPC and PIL special precautions and warnings are included.
High susceptibility to infections	With the suppression of BM function, infections frequently occur and bleeding problems may develop. Intensive supportive therapy is required for the patient to survive this period. Leukocytes are cells of the immune system involved in defending the body against infectious disease. Due to the myelosuppression and especially leukopenia caused by m-AMSA, the risk of infection is increased during m-AMSA treatment.	In the SPC and PIL special precautions and warnings are included. During the induction phase the patients should be kept under close observation and laboratory monitoring in a hospital. Transfusions of leukocytes, erythrocytes and platelets should be available. Potassium level in serum, ECG and hepatic and renal function should be controlled regularly.
Gastro-intestinal adverse drug reactions	Nausea and vomiting are almost universal with m-AMSA treatment, but are generally not severe and can usually be controlled with the use of antiemetic (medicinal product that prevents nausea).	In the SPC and PIL information on the risk of gastro-intestinal adverse drug reactions are included.
Hypersensitivity/ allergic reactions	Allergic reactions are very rare with m-AMSA, but urticaria (nettle rash) and anaphylactic reactions (severe allergic reactions) may occur. Urticaria and rash have also been	In the SPC and PIL information on the risk of hypersensitivity are included.

Risk	What is known	Preventability
	reported.	
Cardiac toxicity	The cardiac toxicity of m-AMSA has been reported to be significantly less common than for other cytostatics and to occur mainly in association with low serum values for potassium.	Cardiac toxicity is prevented by closely monitoring the cardiac function during treatment. The serum values for potassium are controlled before treatment and corrected if needed and are monitored during treatment. In the SPC and PIL special precautions and warnings are included.
Cytostatic extravasation	Infrequently, m-AMSA is reported to cause local necrosis after extravasation (leakage of intravenous medicinal products from the vein into the surrounding tissue) and cytostatic extravasation has been reported as a serious complication of long-term venous access.	In the SPC and PIL information on the risk of cytostatic extravasation is included.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Medication error	m-AMSA infusion shall be prepared before administration by mixing different components. There is a possible risk of preparation failure done by the health care professionals preparing the medication.
Interactions with other drugs	When m-AMSA is administrated it will be found in the blood bound to proteins. Concomitant treatment with other drugs, which also binds to the same proteins may cause that the concentration of m-AMSA will be higher than expected and thereby cause adverse drug reactions related to overdosing.
Lactation	It is not clear whether m-AMSA is excreted in the breast milk for which reason m-AMSA treatment during lactation is contraindicated. Breastfeeding should be discontinued before treatment.
Pregnancy	Data from the use of amsacrine in pregnant women are not available to judge possible harmfulness. However, harmful pharmacological effects during pregnancy are possible. Studies in animals have shown teratogenicity and other reproductive toxicity. 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.
Paediatric population	No relevant information regarding the effect of age on the pharmacokinetics or tolerability of amsacrine is available. Thus, amsacrine is not authorised for use in the paediatric population.

Risk	What is known (Including reason why it is considered a potential risk)
Overdosing	There is a potential risk of overdosing by accident or by medication error as described above.
Reproductive system, congenital, familial and genetic disorders in patients in the reproductive age	m-AMSA treatment of both females and males in the reproductive age may cause problems as there is a potential risk that m-AMSA causes damage to germ cells. Due to the mechanism of action of amsacrine and possible adverse effects on the foetus, women of childbearing potential have to use effective contraception during and up to 3 months after treatments and males during and up to 6 months after treatment. Reversible azoospermia in humans has been described. Although there is not conclusive data, some reports suggest that amsacrine can affect fertility in males.
Patients with impaired liver and/or impaired renal function	Since m-AMSA is metabolized and excreted by way of the liver and kidneys, impaired liver and renal function may lead to delayed excretion of the drug and thereby increased toxicity.

Important missing information

Elderly	With age increases the predisposition of multiple diseases. No relevant information regarding the effect of age on the pharmacokinetics or tolerability of amsacrine is available.
Porphyria	Amsacrine has been suggested as possibly porphyrinogenic in the Drug Database for Acute 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 those. An abbreviated version of this in lay language is provided in the form of the patient information leaflet (PIL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Patient Information Leaflet for AMEKRIN are public available.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

There is no post authorisation development plan in place for AMEKRIN.

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

Major changes to the Risk Management Plan over time are listed in table below.

Version	Date	Safety Concerns	Comment
Version 1.0	01-12-2015	Identified Risks: 5 Potential Risks: 6 Missing information: None	First version of the RMP submitted within the registration procedure.