Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Amsalyo 75 mg powder for concentration for solution infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 75 mg amsacrine.
After reconstitution, each ml of solution contains 1.5 mg amsacrine.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

Red-orange lyophilized powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Salvage therapy of refractory/relapsed acute myeloid leukaemia (AML) in adults, in combination with other chemotherapeutic agents.

4.2 Posology and method of administration

Posology
Treatment should be supervised by a physician experienced in the management of patients with AML. Before treatment is started the potassium level in serum must be controlled and corrected. A serum potassium level >4 mEq/L prior to administration is recommended. Amsacrine is given in combination with other cytostatic drugs.

Numerous dose levels and dosing schedules exist and depend on concomitant therapy, patient and disease characteristics, bone marrow reserve and hematoxicity, and response to therapy. Refer to the protocol by which the patient is being treated and to applicable guidelines. Dosing schedules reported for induction treatment with combination chemotherapy typically include doses of 90 to 150 mg/m2 per day, for three to five consecutive days. For consolidation treatment, lower doses may be considered.

Renal impairment
Caution is advised when administering amsacrine to patients with renal impairment, see section 5.2.In patients with mild renal dysfunction (GFR 60–89 ml/min/1.73 m^2), no starting doseadjustment is recommended.In patients with moderate or severe renal impairment (GFR <59 ml/min/1.73 m^2), a starting dose reduction by approximately 20-30% should be considered. Subsequent dose adjustments may be needed based on clinical toxicity.

Hepatic impairment:
Caution is advised when administering amsacrine to patients with hepatic impairment, see section 5.2. In patients with mild liver dysfunction no dose adjustment is necessary. In patients with moderate or severe hepatic impairment, a starting dose reduction by approximately 20-30% should be considered. Subsequent dose adjustments may be needed based on clinical toxicity.

Elderly
No relevant information regarding the effect of age on the pharmacokinetics or tolerability of amsacrine is available.

Paediatric 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.

Treatment control

During the induction phase the patients should be kept under close observation and laboratory monitoring in a hospital. Transfusions of erythrocytes and platelets should be available. Potassium level in serum, ECG and hepatic and renal function should be controlled regularly.

Method of administration
Administration is performed exclusively as an intravenous infusion in at least 60 minutes to prevent local irritation (risk of phlebitis).

In case of daily or continuous infusion over 24 hours, the placement of a central catheter is advised to prevent the risk of veinitis.
In the case of extravasal administration it is recommended to rinse with a small amount of glucose solution 50 mg/mL after which the body part should be immediately cooled down. The infusion shall be stopped and started in a different vessel.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to amsacrine or acridine derivates or to any of the excipients listed in section 6.1;
- Clear bone-marrow-suppression as a result of treatment with cytostatics or radiotherapy;
- Breast-feeding.

4.4 Special warnings and precautions for use

Bone marrow suppression
Amsacrine can cause severe bone-marrow-depression, thus frequent blood control is necessary. Infections and haemorrhages can be fatal. With an already existing bone-marrow-depression caused by drugs, amsacrine should be administered cautiously and with extra controls. Also if a too strong decrease in white blood cells or blood platelets occurs, interruption of the amsacrine treatment or decrease of dosage can be necessary. Red blood cells and platelets should be available for transfusion as well as other facilities for the treatment of bone-marrow-depression.

Hyperuricaemia
Amsacrine can induce hyperuricaemia secondary to rapid lysis of neoplastic cells. Careful monitoring of blood uric acid levels is recommended, in particular with regard to possible consequences for renal function. Consideration may be given to reducing uric acid levels prophylactically, prior to or concurrent with amsacrine treatment.

Patients with hepatic or renal impairment
Toxicity at recommended doses is enhanced by hepatic or renal impairment. Laboratory evaluation of hepatic and renal function is necessary prior to and during administration. The hepatic monitoring should include serum bilirubin, transaminases (GOT and GPT) and alkaline phosphatase. Laboratory tests of liver function are recommended before (preferentially 24 hours) and regularly during the administration of amsacrine. In addition, serum potassium should be >4 mEq/L prior to administration.

Adverse reactions
The physician should be aware of allergic reactions (anaphylaxis, oedema and skin reactions), GI problems and epileptic insults (epileptic seizures related to the use of amsacrine, can be treated according to standard regimen). Local necrosis can occur with extravasation of amsacrine (see section 4.8). Injection site irritation can be prevented by diluting amsacrine in a greater volume 5 % glucose and infusion is spread over a larger period of time (minimal 1 hour).

Cardiac function
Careful monitoring of cardiac rhythm is recommended for detection of cardiotoxicity. Patients with hypokalaemia are at increased risk of ventricular fibrillation. The risk of developing arrhythmia can be minimized by ensuring a normal serum potassium level immediately, prior to and during amsacrine administration.
Hypokalaemia should be corrected prior to amsacrine administration.

Transient hypomagnesemia may contribute to the risk of cardiac arrhythmia. It is recommended to correct serum magnesium levels prior to amsacrine administration.

Porphyria

Amsacrine has been suggested as possibly porphyrinogenic in the Drug Database for Acute Porphyria.

Laboratory tests
Complete blood counts, liver and renal function tests, and electrolytes should be performed regularly. Electrolytes should be re-evaluated before each day's treatment.

In patients at risk for tumour lysis syndrome (TLS) (e.g. elevated pre-treatment uric acid, compromised renal function or use of nephrotoxic drugs), pre-treatment evaluation is recommended. Laboratory tests of renal function are recommended before (preferentially 24 hours) and during the administration of amsacrine.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions:

Vaccines
Concomitant influenza or pneumococcal vaccination and immunosuppressive therapy have been associated with impaired immune response to the vaccine. In general, all types of live vaccines should be avoided during treatment with amsacrine.

Other cytotoxic agents:
Adverse effects may be potentiated by use with other cytotoxic agents.

Pharmacokinetic interactions

Effect of other medicinal products on the pharmacokinetics of amsacrine

The effect of other medicinal products on the pharmacokinetics of amsacrine has not been studied. Amsacrine is extensively metabolised, but the identity of the catalysing enzymes and transporters are unknown. If possible, concomitant use of strong enzyme inhibitors or inducers should be avoided.

Effects of amsacrine on the pharmacokinetics of other medicinal products

It has not been studied whether amsacrine could act as an enzyme inhibitor or inducer. Thus, other medicinal products should be used with caution together with amsacrine.

Studies in animals indicate that amsacrine may inhibit the metabolism of methotrexate resulting in increased methotrexate exposure, but the clinical relevance of this observation is not known.

4.6 Fertility, pregnancy and lactation

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 (see section 5.3). 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.
The patient should be informed of the potential hazard to the foetus.

Contraception in males and females
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.

Breastfeeding
It is unknown whether amsacrine is excreted in human milk. Breast-feeding is contraindicated during treatment with amsacrine.

Fertility
Reversible azoospermia in humans has been described. Although there is not conclusive data, some reports suggest that amsacrine can affect fertility in females.

4.7 Effects on ability to drive and use machines

No data about this influence are known. In view of reported adverse effects profile patients are advised after administration of amsacrine to be cautious when driving or using machines.

4.8 Undesirable effects

The most common adverse reactions are nausea and/or vomiting, anaemia, fever and infection. Pain or phlebitis on infusion has been reported.

All patients treated with a therapeutic dosage of amsacrine show bone marrow depression. Main complications are infections and haemorrhages. Minimal white blood cells occur on day 5-12, usually followed with complete recovery on day 25. The pattern of inhibition of blood platelets is similar to that of leucocytes.

In the table below all adverse reaction are presented according to MedDRA system organ class and frequency, very common (≥1/10); common (≥ 1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10.000 to <1/1000); not known (cannot be estimated from the available data).

Infections and infestations	
Common	Infection
Blood and lymphatic system disorders	
Common	Thrombocytopenia, pancytopenia, haemorrhage
Rare	Anaemia, granulocytopenia, leukopenia
Immune system disorders	
Rare	Hypersensitivity, anaphylactic reaction, oedema
Metabolism and nutrition disorders	
Common	Hypokalaemia
Rare	Weight decreased, weight increased
Not known	Hyperuricaemia
Psychiatric disorders	
Common	Affect lability
Rare	Lethargy, confusion
Nervous system disorders	
Common	Grand mal seizure[1]
Rare	Headache, hypoaesthesia, dizziness, peripheral neuropathy
Eye disorders	
Rare	Visual disturbances
Cardiac disorders	
Common	Cardiotoxicity, arrhythmia, congestive heart failure[2]
Rare	Atrial fibrillation, sinus tachycardia, ventricular fibrillation[3], ventricular arrhythmias, cardiomyopathy, bradycardia, ECG abnormal, ejection fraction decreased
Vascular disorders	
Very common	Hypotension
Respiratory, thoracic and mediastinal disorders	
Common	Dyspnoea
Gastrointestinal disorders	
Very common	Nausea, vomiting (mild to moderate), diarrhoea, abdominal pain, stomatitis[4]
Common	Gastrointestinal bleeding
Hepatobiliary disorders	
Common	Hepatitis, jaundice, hepatic insufficiency (see section 4.2)
Skin and subcutaneous tissue disorders	
Very common	Purpura
Common	Alopecia, urticaria and rash
Renal and urinary disorders	

Common	Haematuria
Rare	Anuria, proteinuria, acute renal insufficiency
General disorders and administration site conditions	
Very common	Infusion site phlebitis
Common	Pyrexia, Injection site irritation, necrosis, skin inflammation[5]
Investigation	
Very common	Hepatic enzymes increased (see section 4.4).
Rare	Blood bilirubin increased, blood urea increased, blood alkaline phosphatase increased, blood creatinine increased

[1] Sometimes paired with hypokalaemia
[2] especially in paediatric patients, pre-treated with anthracyclines
[3] Fatal or life-threatening, usually in patients with hypokalaemia
[4] Mucosa of mouth and tractus digestivus are frequently effected ranging in severity from mild to life-threatening. Total oral mucosa can be affected; recovery takes several weeks.
[5] Related to the concentration of amsacrine infused (see section 4.4)

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system: HPRA Pharmacovigilance; website: www.hpra.ie.

4.9 Overdose

No specific antidote is known in case of overdosage. Treatment should be symptomatic and supportive.
Haemorrhage and infection, resulting from bone marrow hypoplasia or aplasia, may require intensive supportive treatment with red cell, granulocyte or platelet transfusions and appropriate antibiotics.
Vigorous symptomatic treatment may be necessary for severe mucositis, vomiting or diarrhoea.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic and immunomodulating agents, other antineoplastic agents
ATC code: L01XX01

Amsalyo contains amsacrine which is a synthetic acridine derivative with cytostatic effect. The substance is a strong tissue irritant. The mechanism of action is not totally clarified but is ascribed to the ability of the substance to bind to DNA. Amsacrine inhibits the synthesis of DNA, while the synthesis of RNA is unaffected. It has been shown in cell cultures that cells during division are two to four times more sensitive than resting cells. The dose limiting toxcicity is due to bone marrow depression, therefore Amsalyo is especially suitable in the treatment of acute leukaemia. In clinical studies no cross resistance with anthracycline antibiotics was seen. Amsalyo can be given in combination with cytarabine.

5.2 Pharmacokinetic properties

Distribution
Intravenous infusion of 90 mg/m^2 over 1 hour results in a maximal plasma concentration of 4.8 micrograms/ml. The degree of plasma protein binding is approximately 97%, and the apparent volume of distribution 70-110 L/m^2 .

Biotransformation
Amsacrine is extensively metabolised in the liver,but the identity of catalysing enzymes is largely unknown. The major route of metabolism of amsacrine is oxidation to the reactive quinoen diimine intermediate followed by conjugation with GSH at the C-5`- and C-6`- postitions of the anilino ring.

Elimination
Excretion occurs to a high extent via the bile mainly as 5´- and 6`-GSH metabolites, and as metabolites in urine**.** The elimination is biphasic with a terminal halflife of 6-9 hours. A limited fraction of the dose (≈10%) is excreted unchange in the urine. The rest of the dose is excreted as metabolites in bile and urine. The total plasma clearance rate is 200–300 mL/min per m^2.Within 72 hours approximately 40% of the given dose is found in the urine, as metabolites or as unchanged substance.

Renal and hepatic impairment
Increased halflife is seen in patients with impaired liver function. Urinary excretion of unchangedamsacrine over 72 h, typically around 12% of the dose, has been reported to decrease to only 2% in patients with renal impairment and increase to 20% in patients with hepatic impairment. After administration of [^{14}C]amsacrine, the total amount of radiolabel excreted in urine was 35% in patients with normal organ function, 49% in patients with liver impairment and 2–16% in patients with renal impairment.

5.3 Preclinical safety data

Amsacrine is known to produce its toxic effects mainly due to its myelosuppressive properties. Repeated administration also causes gastrointestinal and mucosal adverse effects in animals.

Because Amsacrine interferes with DNA synthesis, it has potent genotoxic and cytotoxic properties, and the substance is categorised as a class 2B carcinogen to humans by WHO and IARC. Amsacrine is slightly genotoxic in both non-human and human mammalian cells. Carcinogenesis studies of Amsacrine in rats indicate an increased incidence of small intestinal adenocarcinomas and in female rats significantly increased incidences of mammary tumours.

Amsacrine has been shown to induce aneuploidy and killing of differentiating spermatogonia in mice, and to be embryotoxic, fetotoxic and teratogenic in rats. These results provide a basis for genetic counselling of patients under Amsacrine therapy and recommendation for contraception in both males and females.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactic acid

6.2 Incompatibilities

Solutions other than glucose may not be used during preparation of the medicinal product as described in section 4.2, since amsacrine is incompatible with chloride ions.
This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years.
After reconstitution: the physical and chemical stability of the product has been demonstrated for five days at 25°C. However, from a microbiological point of view, the product must be used immediately. If the product is not used immediately, the storage times and conditions after reconstitution and before use are solely the responsibility of the user.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Powder in a 50 ml vial (type I brown glass) with a stopper (bromobutyl); box of five.

6.6 Special precautions for disposal and other handling

The following is required in addition to the usual precautions to preserve the sterility of preparations for injection:
- wear a long-sleeve tight cuff laboratory coat, in order to prevent any projection of the solution on the skin,
- also wear a disposable surgical mask and wrap-around safety eyeglasses,
- wear disposable PVC gloves, not latex, after aseptically washing the hands,
- prepare the solution on a work liner,
- stop the infusion in case of injection outside the vein,

- dispose of any material used for the preparation of the solution (syringes, compresses, liners, vial) in a container reserved for this purpose,
- destroy the toxic waste,
- handle excreta and vomit with care.

Pregnant women must avoid handling cytotoxic agents.

After introducing 50 ml of water for injectable preparation into the vial containing lyophilisate, it is essential to mix the vial gently, without shaking, and let it stand for approximately 15 minutes. If necessary, repeat until a clear solution and an intense orange colour is obtained. For stability of reconstituted solution see section 6.3.

The solution prepared should only be injected IV, in the form of an infusion. To prepare the infusion, remove 50 ml of the 500 ml isotonic glucose serum bag and replace with the reconstituted amsacrine solution.
Salt isotonic saline should not be used (risk of precipitation of amsacrine).

Cytostatics should be handled in accordance with national requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Eurocept International BV
Trapans 5
1244 RL Ankeveen
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA1591/003/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26th January 2024

10 DATE OF REVISION OF THE TEXT