SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Amekrin 75 mg/1.5 ml concentrate and solvent for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of concentrate for solution for infusion contains 50 mg amsacrine.
Each vial of 1.5 ml of concentrate for solution for infusion contains 75 mg amsacrine.
Each ml concentrate after the first dilution with the solvent contains 5 mg amsacrine.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate and solvent for concentrate for solution for infusion.
The concentrate is a clear bright orange/red liquid, the pH of the concentrate is between 3.50 – 4.50.
The solvent is a clear solution, the pH of the solvent is between 2.50 – 3.50.

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 with Amekrin should be introduced by or in cooperation with a doctor experienced in treatment with cytostatics. Before treatment is started the potassium level in serum must be controlled and corrected. Amekrin is given in combination with other cytostatics.Serum potassium level >4 mEq/L prior to administration is recommended.

Induction phase: Optimal dose is individual and dependent on the combination. Usual dose per treatment period is 300-650 mg/m^2 and is divided over 3-7 days. The total dose during a treatment period should not exceed 750 mg/m^2. In order to achieve remission more than one treatment period may be necessary.
Consolidation /Maintenance phase: Comparable or somewhat lower doses compared with the induction phase are given.

Renal impairment
Caution is advised when administering amsacrine to patients with renal impairment. In patients with mild-renal dysfunction, no starting dose adjustment is recommended. In patients with moderate or severe renal impairment, 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. 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
Intravenous use.
Amekrin must be diluted in 500 ml glucose solution and be administered as an intravenous infusion over 1-2 hours. At doses of 125 mg/m^2 or higher the duration of infusion should be at least 90 minutes.

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

Solutions other than glucose may not be used, Amekrin is incompatible with chloride ions.
Only glass syringes must be used when removing and transferring the concentrated solutions.

Caution in the handling and preparation of the solution should be excercised, 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;
- Lactation.

4.4 Special warnings and precautions for use

Amsacrine should only be used under strict control of a specialised oncologist, with preference in institutions with experience with this kind of therapies.

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 tumor 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 amsacrine

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 antracyclines

[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 listed in Appendix V*.

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

Amekrin 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 Amekrin is especially suitable in the treatment of acute leukaemia. In clinical studies no cross resistance with anthracycline antibiotics was seen. Amekrin 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 unchanged amsacrine 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 ~~is~~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 tumors.

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 counseling of patients under Amsacrine therapy and recommendation for contraception in both males and females.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Concentrate for solution for infusion:
N,N-dimethylacetamide

Solvent:
Lactic acid,
water for injections.

6.2 Incompatibilities

Amsacrine is incompatible with chloride ions. Sodium chloride solutions may not be used. This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Only glass syringes may be used when removing and transferring the concentrated solutions. See section 6.6 *Special precautions for disposal and other handling.*

6.3 Shelf life

2 years.

Diluted solution (mixed concentrate and solvent, before further dilution):
The diluted solution should be used immediately for further dilution. However the chemical and physical in-use stability has been demonstrated for 48 hours when stored at 2° C – 25° C. If stored for 24-48 hours the diluted solution should be further diluted and used immediately.

Solution for infusion:
Chemical and physical in-use stability of the solution for infusions has been demonstrated for 48 hours at 2° C – 25° C. The chemical and physical in-use stability for the diluted solution from first dilution and the further diluted solution for infusion has not been demonstrated for more than a total of 48 hours.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 25º C.

For storage conditions of the diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

Concentrate for solution for infusion: 3.2 ml glass vial (each vial of 1.5 ml of concentrate for solution for infusion contains 75 mg amsacrine), Ph. Eur. glass type I, clear glass, Flurotec® coated bromobutyl injection stopper with a yellow aluminium flip-off seal.
Solvent: 20 ml glass vial (each vial of solvent contains 13.5 ml of a solution of lactic acid in water for injection as a clear solution), Ph. Eur. glass type I, clear glass, chlorbutyl stopper with an aluminium flip-off seal.

Packsize 1 x 6 vials of concentrate for solution for infusion and 6 vials of solvent for solution for infusion.

6.6 Special precautions for disposal and other handling

Preparation of the medicinal product
The concentrate for solution for infusion must be diluted with the enclosed solvent. The appearance of the diluted solution is a clear orange solution, free of particulates.
The diluted solution is then added to at least 500 ml glucose 50 mg/ml. The appearance of this solution is a clear orange solution, free of particulates.

Solutions other than glucose may not be used.

Only glass syringes may be used when removing and transferring the concentrated solutions.
1.5 ml of the concentrate for solution for infusion is transferred aseptically to the injection bottle containing the solvent and is gently shaken until a clear solution is obtained (concentration of the solution is 5 mg/ml amsacrine).
75 mg, 90 mg and 120 mg amsacrine corresponds to 15 ml, 18 ml and 24 ml diluted solution, respectively.

Note: the diluted solution may not be injected before it has been further diluted with at least 500 ml glucose solution 50 mg/ml.

Handling
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.

In case the solution comes into contact with eyes or mucous membranes rinse with plenty of water and in contact with the skin immediately wash thoroughly with soap and water. If irritaion persists after washing you must contact a doctor. In the case of extravasal administration rinse with a small amount of glucose solution 50 mg/ml after which the body part is immediately cooled down. The infusion is stopped and started in a different vessel.

7. MARKETING AUTHORISATION HOLDER

Eurocept International BV
Trapgans 5
1244RL Ankeveen
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be completed nationally

10. DATE OF REVISION OF THE TEXT

2021-03-25