Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Amsidine 50mg/ml Concentrate and Solvent for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 75mg amsacrine in 1.5ml (50mg per ml).

Each solvent vial contains 13.5ml of Lactic Acid and water for injection to give a concentration of 0.0353M L-Lactic acid.

Each ml of the combined solution of the concentrate when diluted with the solvent contains 5mg amsacrine per ml

For a full list of exipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate and solvent for solution for Infusion.

Concentrate is a clear, bright orange/red coloured solution and solvent for infusion is clear colourless solution.

The pH of the combined solution is 3.5 - 4.5.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Amsidine is indicated for the induction and maintenance of remission in acute leukaemia of adults. It is effective in patients refractory to the anthracycline antibiotics used singly or in combination with other chemotherapeutic agents, and in patients who were formerly treated with maximum cumulative doses of these antibiotics.

4.2 Posology and method of administration

Intravenous infusion

Amsidine must be diluted in 500ml 5% Dextrose Injection BP and infused over 60 to 90 minutes. Phlebitis or pain at the injection site may occur at doses greater than 70 mg/m^2. (NOTE: DO NOT USE OTHER DILUENTS. AMSIDINE IS **INCOMPATIBLE** WITH **SALINE**). Care must be taken that no extravasation occurs which might produce severe irritation or necrosis. Caution in the handling and preparation of the solution should be exercised, and the use of polyethylene gloves is recommended. If the solution of Amsidine contacts the skin or mucosae, immediately wash thoroughly with soap and water.

Adults

Induction of remission phase
The usual dosage of Amsidine in the induction phase is 90mg/m^2 every day for five consecutive days (total dose 450 mg/m^2 per course of treatment). If bone marrow biopsy performed on day six displays over 50% cellularity and the blasts count is over 30%, the treatment may be extended for an additional three days, bringing the total dose per course of treatment to 720 mg/m^2.

More than one course of treatment may be required to achieve induction. Depending on the effectiveness of the first course in producing myelosuppression, the subsequent courses are given at two-week (if not effective) to four-week (if effective) intervals. In cases where a hypocellular marrow has not been achieved after the first course of treatment, the daily dose of Amsidine may be escalated to 120 mg/m^2 per day for the subsequent courses, provided that this is not contra-indicated for reasons of non-myelosuppressive toxicity.

For patients with impaired liver function or impaired renal function, the dose of Amsidine should be decreased by 20-30% (to 60-75 mg/m^2 per day).

Maintenance phase
The maintenance dose is about one third the induction dose, given either as a single IV infusion or divided in three daily doses e.g. 150 mg/m^2 given once every 3-4 weeks or 50 mg/m^2 per day for three consecutive days, repeated every 3-4 weeks.

Each maintenance course should bring down the granulocyte count to 1,000-1,500/µl and Platelet count to 50,000 - 100,000/µl. The granulocyte and platelet counts should be allowed to recover between the courses to over 1,500/µl abd 100,000/µl respectively; otherwise the subsequent course should be delayed.

Elderly
Elimination may be slower in this group. This should be considered when designing dose schedules for the elderly.

Children under 12 Years
Not recommended.

4.3 Contraindications

- Hypersensitivity to amsacrine or acridine derivates;
- Hypersensitivity to one of the other ingredients of the product;
- 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 hemorrhages 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.

Hyperuricemia
Amsacrine can induce hyperuricemia 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. A dose reduction might be considered.

Adverse reactions
The physician should be aware of allergic reactions (anaphylaxia, 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 hypokalemia are at increased risk of ventricular fibrillation. The risk of developing arrhythmias can be minimized by ensuring a normal serum potassium level immediately prior to and during amsacrine administration.
Hypokalemia should be corrected prior to amsacrine administration.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Vaccines:
Concomitant influenza or pneumococcal vaccination and immunosuppressive therapy have been associated with impaired immune response to the vaccine.

Other Protein-binding Drugs:
Amsacrine may be displaced from serum albumin, with consequential increase in free drug and toxicity if used with other highly protein binding drugs.

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

4.6 Fertility, pregnancy and lactation

Data on the usage of this compound during pregnancy in patients are not available to judge possible harmfulness. However based on its pharmacologic activity harmfulness of treatment during pregnancy is possible.

In animal studies teratogenicity and other reproductivity toxicity has been observed (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.

Contraception in males and females
Due to the mechanism of action of amsacrine and possible adverse effects on the foetus, females should use effective contraception for 3 months after treatments and males for 6 months after treatment.

Fertility
Reversible azospermia in humans has been described.

Lactation
As it is not clear whether amsacrine is excreted in the mother milk, lactation is contraindicated.

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, anemia, 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 hemorrhages. 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 events are presented according to classification of organ system 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, hemorrhage
Rare	Anemia, granulocytopenia, leukopenia
Immune system disorders	
Rare	Hypersensitivity, anaphylactic reaction, oedema
Metabolism and Nutrition Disorders	
Common	Hypokalemia
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, hypoesthesia, dizziness, periferal 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

Not known	Cardiac arrest
Vascular Disorders	
Very common	Hypotension
Common	Hemorrhage
Respiratory, Thoracic and Mediastinal Disorders	
Common	Dyspnea
Gastrointestinal Disorders	
Very common	Nausea, vomiting (mild to moderate), diarrhea, abdominal pain, stomatitis[4]
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	Hematuria
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 hypokalemia

[2] especially in paediatric patients, pretreated with antracyclines

[3] fatal or lifethreathening, usually in patients with hypokalemia

[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)

4.9 Overdose

No specific antidote is known in case of overdosage. Treatment should be symptomatic and supportive.

Hemorrhage and infection, resulting from bone marrow hypoplasia or aplasia, may require intensive supportive treatment with red cell, granulocyte or platelet transfusions and appropriate antibiotics.
Vigourous symptomatic treatment may be necessary for severe mucositis, vomiting or diarrhea.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Amsidine is a sterile antitumour chemotherapeutic agent for intravenous infusion. Although not completely clarified, the mode of action of amsacrine is related to its property of binding the DNA through intercalation and external (electrostatic) forces. Amsacrine inhibits the synthesis of DNA while the RNA may not be directly affected. An additional mode of action, involving modification of cell membrane function, has been suggested.

5.2 Pharmacokinetic properties

Amsidine is administered by intravenous infusion. Amsidine has a low lipid solubility, and a relatively high molecular weight, so that it is unlikely that it would cross the blood-brain barrier. Amsidine distributes well in the body, except to the brain and CSF, and is therefore inactive against cerebral tumours.

Studies have shown that the plasma concentration time profiles of Amsidine in man are best described using a three compartment open model. The terminal half-life was found to be prolonged in patients with severe hepatic dysfunction. Work in animals has shown that after biotransformation in the liver, the metabolites of Amsidine are finally excreted in the bile by an active transport mechanism. The majority of Amsidine is excreted in its metabolised form. Studies in man have shown that 20% of the administered drug (free and metabolised) was eliminated in the urine within the first 8 hours, and a total of about 42% within 72 hours in one patient with normal renal function.

5.3 Preclinical safety data

No additional data of relevance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Concentrate
N,N Dimethylacetamide

Solvent
L-lactic Acid
Water for Injection

6.2 Incompatibilities

Amsidine is incompatible with saline. Amsidine in solution reacts with plastic syringes.
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened: Amsacrine concentrate vial: - 12 months
Unopened: Solvent vial: - 12 months

Once opened and diluted with Amsidine solvent: Chemical and physical in-use stability of the reconstituted and diluted drug has been demonstrated for 8 hours when stored below 25^{o}C and protected from sunlight. Unused solution should be discarded.

From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the product should be used immediately after first opening or following reconstitution. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Do not store above 25^{o}C.

Store in the original pack in order to protect from light and moisture.

6.5 Nature and contents of container

Concentrate vial - 2ml clear Type I, Ph. Eur. neutral glass vial containing 1.5ml amsacrine solution.
Solvent vial - 20ml clear Type I, Ph. Eur. neutral glass vial contains 13.5ml of 0.0353M L-lactic acid.

Each carton contains 6 vials of concentrate and 6 vials of solvent.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Amsidine should be handled in accordance with local hospital guidelines for handling cytotoxic drugs. Any unused product or waste material should be disposed of in accordance with local requirements.

Preparation of the medicinal product: 1.5ml of the drug solution is withdrawn from the concentrate vial and added to the solvent vial. The diluted concentrate is further diluted with 500ml of 5% Dextrose Injection BP solution. The concentration when diluted with 500ml of 5% Dextrose solution is 0.146mg Amsacrine per ml.

Use immediately once diluted further with 500ml of 5% Dextrose Injection BP.

Appearance of the diluted solution: The diluted solution is clear deep orange red solution.

Dextrose 5% Injection BP must be used for dilution of Amsidine. Other diluents should not be used.

Caution in handling and preparation of the solution should be excercised, and the use of polyethylene gloves is recommended (see patient information leaflet). If the solution of Amsidine contacts the skin or mucosae, immediately wash thoroughly with soap and water.

Glass syringes must be used as Amsidine in solution reacts with plastic syringes.

Do not use the solution if the contents are discoloured in any way or contains particles in it.

7 MARKETING AUTHORISATION HOLDER

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DK-2820
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