

SUMMARY OF PRODUCT CHARACTERISTICS

1. Trade Name of the Medicinal Product

Amsidine Concentrate for Infusion

2. Qualitative and Quantitative Composition

Each ampoule contains 75mg amsacrine in 1.5ml(50mg per ml).
Each solvent vial contains 13.5ml of 0.0353M L-Lactic Acid.

3. Pharmaceuticals Form

Concentrate and solvent for infusion.

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

Clinical Particulars

4.1 Therapeutic Indication

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/m². (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 90 mg/m² every day for five consecutive days (total dose 450 mg/m² 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/m².

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/m² per day for the subsequent courses, provided that this is not contraindicated 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/m² 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. 150mg/m² given once every 3-4 weeks or 50mg/m² 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/ μ l and the platelet count to 50,000-100,000/ μ l. If this is not accomplished, the maintenance dose may be escalated by 20% every second course. The granulocyte and platelet counts should be allowed to recover between the courses to over 1,500/ μ l and 100,000/ μ l 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 Contra-indications

Amsidine treatment should not be started in patients who have pre-existing marked bone marrow suppression induced by other chemotherapeutic agents or radiotherapy.

4.4 Special Warnings and Precautions for Use.

Patients should be hospitalised during the induction phase of treatment for close observation and extensive laboratory monitoring. Amsidine should be used only by physicians experienced in cancer chemotherapy.

With recommended dose schedules, leucopenia is usually transient, reaching its nadir at 10-13 days after treatment, with recovery usually following by the 17th to 25th day. White blood cell counts of 1000/ μ l or lower are to be expected during treatment with appropriate doses of Amsidine. Doses higher than recommended may produce more severe or more prolonged marrow suppression.

Periodic monitoring of bone marrow, cardiac, liver, kidney and CNS functions should be carried out in patients receiving Amsidine and particularly in those with pre-existing disorders of these systems. In the case of an exceedingly large fall in white cell count and excessive depression of bone marrow, suspension of treatment or reduction of dosage may be necessary.

Pharmaceutical Precautions: Caution in handling and preparation of the solution should be exercised, and the use of polyethylene gloves is recommended (see enclosure leaflet). If the solution of Amsidine contacts the skin or mucosae, immediately wash thoroughly with soap and water. Amsidine must be diluted in 500ml 5% Dextrose Injection BP and infused over 60 to 90 minutes (Note: do not use other diluents, Amsidine is incompatible with saline). The solution when diluted for infusion is stable for eight hours at room temperature. It should be protected from exposure to sunlight, and any unused solution should be discarded. (see enclosure leaflet). Glass syringes must be used as Amsidine in solution reacts with plastic syringes.

The labelling contains the following statements: avoid contact with the skin and keep out of the reach of children.

4.5 Interactions with Other Medicaments and Other Forms of Interaction.

None known.

4.6 Pregnancy and Lactation.

Animal studies have indicated that Amsacrine has foetotoxic and teratogenic properties. In addition there may be an effect on fertility. There is no information on use in human pregnancy, therefore the benefit/risk consideration should be carefully weighed when administering Amsidine.

4.7 Effects on Ability to Drive and Operate Machines.

None known.

4.8 Undesirable Effects.

Studies have demonstrated a mutagenic potential. No carcinogenic studies have been carried out. As with other antineoplastic agents there is a possibility that prolonged use may lead to a carcinogenic effect. This should be borne in mind when undertaking long-term treatment.

Adverse Events.

Haematopoietic System: The dose limiting toxicity associated with Amsidine is myelosuppression and pancytopenia, requiring supportive treatment with white and red blood cells and platelets. Major complications during therapy were infections and haemorrhages treated, respectively, with antibiotics and platelet transfusions.

Gastro-intestinal: Nausea, with or without vomiting occurred frequently, but these symptoms were usually mild to moderate. Mucositis (stomatitis and oesophagitis

was almost as frequent and ranged in severity from mild to life-threatening; its frequency and severity were not strictly dose-related.

Central Nervous System: A few cases of grand mal seizures in acute leukaemia patients have occurred during treatment with Amsidine. These patients were

suffering, however, from a number of conditions related to far-advanced disease and were heavily pre-treated; and it is unclear whether the seizures were attributable to Amsidine. The seizures generally were responsive to standard treatment, such as phenytoin.

Renal: Occasional occurrence of haematuria, anuria and rarely acute renal failure have been reported.

Hepatic: Liver function tests have showed occasional transient elevations of serum bilirubin and alkaline phosphatase, sometimes accompanied by jaundice, which required lowering the dose of Amsidine.

Cardiac: Cardiotoxicity occurred in several patients. It ranged from grand mal seizures followed by ventricular tachycardia to congestive heart failure or cardiac arrest.

Cutaneous: Local tissue irritation, necrosis and phlebitis have been reported. The problem is related to the concentration of drug infused per unit time; it is ameliorated by diluting the drug in a large volume of 5% Dextrose Injection BP and infusing over a longer period of time (1 to 2 hours). Alopecia occurred in about 1 in 7 patients, sometimes precipitously. Since most patients were previously treated with other chemotherapeutic agents/or radiation, it is not clear whether this was a cumulative effect of all treatments.

4.9 Overdose

The treatment of overdosage should be supportive and the blood picture should be closely monitored with appropriate blood transfusions being given if necessary.

5. Pharmacological Properties

5.1 Pharmacodynamic Properties

5.2 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.

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 Pre-clinical Safety Data.

No additional data of relevance.

6. Pharmaceuticals Particulars

6.1 List of Excipients

N,N Dimethylacetamide
L Lactic Acid
Water for Injection

6.2 Incompatibilities

Amsidine is incompatible with saline. Dextrose 5% Injection BP must be used for dilution of Amsidine. Other diluents should not be used. Amsidine in solution reacts with plastic syringes.

6.3 Shelf Life

36 months for 2ml ampoules containing amsacrine solution.
36 months for 20ml vials containing diluent.

(b) The solution when diluted for infusion is stable for 8 hours when stored below 25°C provided it is 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°C. Store in a dry place and protect from light

6.5 Nature and Contents of Container

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

Each pack contains 6 ampoules of active and 6 vials of diluent.

6.6 Instructions for Use/Handling

Amsidine should be handled in accordance with the Pharmaceutical Society guidelines or local hospital guidelines for handling cytotoxic drugs. See attached safety/Hazard data sheet for handling Amsidine. Caution in handling and preparation of the solution should be exercised, and the use of polyethylene gloves is recommended (see enclosure 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.

7. Marketing Authorisation Holder

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8. Marketing Authorisation Number

PA 899/2/1

9. Date of First Authorisation/Renewal of Authorisation

5 March 1994

10. Date of (Partial) Revision of the Text

October 1999