

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1 NAME OF THE MEDICINAL PRODUCT

Amsidine

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1ml contains 50mg of Amsacrine.

### 3 PHARMACEUTICAL FORM

Amsidine is formulated as two sterile liquids combined for administration via intravenous infusion to human beings.

### 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<sup>2</sup>. (**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/m<sup>2</sup> every day for five consecutive days (total dose 450 mg/m<sup>2</sup> 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<sup>2</sup>.

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<sup>2</sup> 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<sup>2</sup> 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/m<sup>2</sup> given once every 3-4 weeks or 50mg/m<sup>2</sup> 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/ $\mu$ l and the platelet count to 50,000-100,000/ $\mu$ 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/ $\mu$ l and 100,000/ $\mu$ 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 Contraindications**

- Hypersensitivity to amsacrine or acridine derivatives;
- 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 ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1000$  to  $< 1/100$ ); rare ( $\geq 1/10.000$  to  $< 1/1000$ ); not known (cannot be estimated from the available data).

<b><i>Infections and Infestations</i></b>	
Common	Infection
<b><i>Blood and Lymphatic System Disorders</i></b>	
Common	Thrombocytopenia, pancytopenia, hemorrhage
Rare	Anemia, granulocytopenia, leukopenia
<b><i>Immune system disorders</i></b>	
Rare	Hypersensitivity, anaphylactic reaction, oedema
<b><i>Metabolism and Nutrition Disorders</i></b>	
Common	Hypokalemia
Rare	weight decreased, weight increased
Not known	hyperuricaemia
<b><i>Psychiatric Disorders</i></b>	
Common	Affect lability
Rare	Lethargy, confusion
<b><i>Nervous System Disorders</i></b>	
Common	Grand mal seizure <sup>1</sup>
Rare	Headache, hypoesthesia, dizziness, periferal neuropathy
<b><i>Eye disorders</i></b>	
Rare	Visual disturbances
<b><i>Cardiac disorders</i></b>	
Common	Cardiotoxicity, arrhythmia, congestive heart failure <sup>2</sup>
Rare	Atrial fibrillation, sinus tachycardia, ventricular fibrillation <sup>3</sup> , ventricular arrhythmias, cardiomyopathy, bradycardia, ECG abnormal, ejection fraction decreased
<b><i>Vascular Disorders</i></b>	
Very common	Hypotension
Common	Hemorrhage
<b><i>Respiratory, Thoracic and Mediastinal Disorders</i></b>	
Common	Dyspnea
<b><i>Gastrointestinal Disorders</i></b>	
Very common	Nausea, vomiting (mild to moderate), diarrhea, abdominal pain, stomatitis <sup>4</sup>
<b><i>Hepatobiliary Disorders</i></b>	
Common	Hepatitis, jaundice, hepatic insufficiency (see section 4.2)

<b><i>Skin and Subcutaneous Tissue Disorders</i></b>	
<sup>1</sup> Very common	Purpura
Common	Alopecia, urticaria and rash
<b><i>Renal and Urinary Disorders</i></b>	
<sup>0</sup> Common	Hematuria
<sup>m</sup> Rare	Anuria, proteinuria, acute renal insufficiency
<b><i>General Disorders and Administration site Conditions</i></b>	
<sup>t</sup> Very common	Infusion site phlebitis
Common	Pyrexia, Injection site irritation, necrosis, skin inflammation <sup>5</sup>
<b><i>Investigation</i></b>	
<sup>m</sup> Very common	Hepatic enzymes increased (see section 4.4).
<sup>e</sup> Rare	Blood bilirubin increased, blood urea increased, blood alkaline phosphatase increased, blood creatinine increased

<sup>1</sup> sometimes paired with hypokalemia

<sup>2</sup> especially in paediatric patients, pretreated with anthracyclines

<sup>3</sup> fatal or lifethreatening, usually in patients with hypokalemia

<sup>4</sup> 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.

<sup>5</sup> 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.

Vigorous 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**

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.

## **6.3 Shelf life**

18 months.

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**

Store in a dry place at a temperature not exceeding 25°C and protect from light.

#### **6.5 Nature and contents of container**

Active vial - 2 ml clear neutral glass vial containing Amsacrine solution 1.5ml.  
Diluent vial - 20 ml clear neutral glass vial containing diluent 13.5ml.

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

#### **6.6 Special precautions for disposal**

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.

## **7 MARKETING AUTHORISATION HOLDER**

NordMedica A/S  
Jægersborg Allé 164  
DK-2820 Gentofte  
Denmark

**8     MARKETING AUTHORISATION NUMBER(S)**

PL 39656/0002

**9     DATE OF FIRST AUTHORISATION/RENEWAL OF THE  
AUTHORISATION**

3 March 1998

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