1. NAME OF THE MEDICINAL PRODUCT

Amsidine, concentrate for solution for intravenous infusion 75 mg/ 1,5 ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

75 mg amsacrine per 1,5 ml concentrate for solution for intravenous infusion.
For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for intravenous infusion.

Description:
Active ingredient in glass ampoule with orange-red liquid.
Solvent in glass vial with colourless liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Acute non-lymphatic leukemia refractory to other treatments.

4.2 Posology and method of administration

Dosage and administration
The usual doseage of amsacrine in the induction phase is 90 mg/ m^2 during 5 succesive days at an infusion rate/day of 30-90 minutes. The total dose per course is 450 mg/ m^2.

If bone marrow biopsy performed on day six displays over 50 % cellularity and the blast count is over 30 %, the treatment may be extended, 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 of a remission. Depending on the effectiviness of the first course the subsequent course can be started after a two-week (if not effective) to four weeks (if effective) interval.
In cases where no hypocellular marrow has been achieved after the first course of treatment, the daily dose of amsacrine may be increased to 120 mg/m^2 for the subsequent courses, unless this is contraindicated for reasons other than bone-marrow toxicity.

Dosage with hepatic or renal insufficiancy
For patients with impaired liver function or impaired renal function, the dose of amsacrine should be decreased by 20-30 %.

Dosage in paedriatics
Experience with amsacrine in children is limited.

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 bloodcontrol is necessary. Infections and haemorrages 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 bloodcells or bloodplatelets occurs, interruption of the amsacrine treatment or decrease of dosage can be necessary. Red bloodcells and platelets should be available for transfusion as well as other facilities for the treatment of bone-marrow-depression.

Hyperuricemia
Amsacrine can induce hyperuricemia secundary to rapid lysis of neoplastic cells. Careful monitoring of blood uric acid levels is recommended. 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 (see section 4.2 Posology and method of administration).

Adverse reactions (see section 4.8 Undesirable effects)
The physician should be aware of allergic reactions (anaphylaxia, oedema and skin reactions), GI problems, epileptic insults and should consider cardiotoxicity, renal insufficiency and hepatic impairment. Local necrosis can occur with extravasation of amsacrine.

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.

Conception
During treatment of man or female, 3 months after treatment of amsacrine for female and 6 months for man, conception should be prevented.
Reversible azospermia in humans has been described See section 4.6 pregnancy and lactation).

Use in children
Safety and activity in children have not yet been established.

4.5 Interaction with other medicinal products and other forms of interaction

Vaccines
Concomittant influenza or pneumococal vaccination and immunosuppressive therapy have been associated with impaired immune response to the vaccine.

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

Other cytotoxic drugs
Adverse events may be potentiated by use with other cytotoxic drugs.

4.6 Pregnancy and Lactation

Pregnancy
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 reproductivitytoxicity 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 the treatment should evaluated towards the possible risks to the fetus.

Lactation
As it is not clear whether amsacrine is excreted in the mothermilk. 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 patient are advised after administration of amsacrine to be cautious when driving or using machines.

4.8 Undesirable effects

The estimated frequencies of adverse events are categorized as follows: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1.000, <1/100); rare (≥1/10.000, <1/1.000); very rare (<1/10.000).

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

Infections and infestations
Common: Infection, fever.

Blood and lymphatic system
All patients treated with a therapeutic dosage of amsacrine show bone marrow depression. Main complications are infections and haemorrhages. Minimal white bloodcells occur on day 5-12, usually followed with complete recovery on day 25. The pattern of inhibition of bloodplatelets is similar to that of leucocytes.
Common: thrombocytopenia, pancytopenia, hemorrhage.
.Rare: anemia, granulocytopenia, leukopenia, fever apparently not related to sepsis.

Immune system disorders
Rare: Allergic reactions amongst them anaphylaxia and edema.

Metabolism and nutrition disorders
Common: Hypokalemia.
Rare: Weight decrease, weight increase.

Psychiatric disorders
Common: emotional lability.
Rare: lethargy, confusion

Nervous system disorders
Common: grand mal seizures, sometimes paired with hypokalemia. The seizures can be treated in the usual way, f.i. with phenytoin.
Rare: headache, hypoesthesia, dizziness and periferal neuropathy.

Eye disorders
Rare: visual disturbances.

Cardiac disorders
Common: Cardiotoxic symptoms, cardiac arrythmia, congestive heart failure (especially in paediatric patients, pretreated with antracyclines).
Rare: atrial fibrillation, sinus tachycardia, fatal or life-threathening ventricular fibrillation (usually in patients with hypokalemia), ventricular arrhythmias, cardiomyopathy, bradycardia, ECG changes, ejection fraction decrease.

Vascular disorders
Very common: Hypotension
Common: haemorrhages.

Respiratory, thoriac and mediastinal disorders
Common: Dyspneu

Gastrointestinal disorders
Very common: Nausea and vomiting (mild to moderate), diarrhea, abdominal pain. 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.

Hepato-biliary disorders
Common: hepatitis, jaundice, hepatic insufficiency (see also section 4.2 Dosage with hepatic and renal insufficiancy).

Skin and subcutaneous tissue disorders
Very common: purpura.
Common: alopecia , urticaria and rash.

Renal and urinary tract disorders
Common: hematuria.
Rare: anuria, proteinuria and acute renal insufficience.

General disorders and administration site disorders
Very common: phlebitis on infusion.
Common: Local tissue irritation, necrosis, cutaneous inflammatory reaction. . This problem is related to the concentration of amsacrine infused. This 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). With extravasation necrosis can occur.

Investigations
Common: Liver function tests show in 20-40 % of the cases transient elevations of hepatic enzymes. If a serious increase is seen, dosage decrease is necessary.
Rare: Increased laboratory values of bilirubin, BUN, alkaline phosphatase, creatinine and ASAT.

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

Pharmacotherapeutic category: antineoplastic agent (ATC-code: L01X X01).

Amsacrine is a synthetic acridine-derivate.Though the mode of action is not fully understood, it is accepted that amsacrine binds to DNA by intercalation and external electrostatic binding. The synthesis of DNA is inhibited. DNA-fragmentation and chromosomal changes occur. RNA-synthesis is not changed.
Clinically no cross resistance has been found with antracycline antibiotics such as doxorubicine and daunorubicine.
Amsacrine gave in refractory patients a remission of short duration in 20-30 % of patients.

5.2. Pharmacokinetic properties

Distribution
Amsacrine is extensively bound to tissue, probably especially to membrane structures. Also there exists a strong binding to plasma proteins which is concentration dependant. In animal experiments amsacrine penetrates the CNS system. The partition volume of amsacrine is about 1,5 - 2 l/kg bodyweight.

Metabolism
Amsacrine is metabolised mainly in the liver.
Plasma-elimination curve shows firstly a fast decline (distribution phase) followed by an elimination phase with a halflife of 6-9 hours. The halflife of the slow phase is considerably longer in patients with hepatic insufficiency (till more than 17 hours). Mild to moderate kidney insufficiency has hardly an effect on pharmacokinetics of amsacrine.

Excretion
Renal clearance of unchaged amsacrine is about 4 % of total body clearance which is 200 - 500 ml/min. Inactive metabolites are excreted with the bile.

5.3 Preclinical safety data

Amsacrine caused embryotoxicity and teratogenicity in rats and mice In view of its mechanism of action, amsacrine should be considered a potential carcinogen and mutagen in man.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

An ampoule contains as solvens dimethylacetamide (DMA).
A vial contains solvens L-lactic acid and water for injection.

6.2 Incompatibilities

The amsacrine solution must only be diluted with the given lactic acid and with 5% glucose. Amsacrine is dissolved in dimethylacetamide (DMA).
As DMA can interact with plastic and rubber, glass syringes should be used in preparing an intravenous solution (see section 6.6. Instructions for use and handling)

N.B.:
1. Do not use other diluents
2. Amsidine is incompatible with saline
3. Amsacrine is dissolved in dimethylacetamide (DMA). As DMA can interact with plastics and rubber, glass syringes must be used; Codan syringes, mentioned under point 5 can be used
4. Glass syringes can be cleaned with aceton.
5. Amsacrine-DMA solution can if necessary be transferred to the vial with lactic acid by means of a 2 cc plastic syringe, trademark "CODAN", if the amsacrine solution is kept in this syringe for not longer than 10 minutes. 20 cc "CODAN" syringes can, if necessary, be used to transfer diluted amsacrine-lactic acid solution to 5 % glucose infusion solution if this solution does not stay longer than 30 minutes in the syringe.
6. Glass infusion bottles or bags with rubber stops must not be used, as an interaction between amsacrine solution and rubber stops cannot be excluded.

6.3 Shelf-Life

3 years.
An infusion solution of maximal 400 mg amsacrine in 500 cc 5 % glucose, stored in PVC or polythene infusion bags and prepared conform above instructions will be stable for 48 hours at room temperature and protected from light.

6.4 Special precautions for storage

Do not store above 25 °C.
Do not store in the refrigerator; do not freeze.

6.5 Nature and contents of container

Box containing 6 glass (type 1) ampoules of Amsidine and 6 glass (type 1) vials of lactic acid.

6.6 Instructions for usage and handling and disposal

General
As with other toxic substances extreme caution should be used in preparation and adminstration of the product. Precautions should be taken in order to prevent exposure to personel during preparation and administration.

Method of handling
During preparation, preferably in vertical laminair airflow cabinet, protective gloves, mouth mask and spectacles should be used, during administration protective gloves (polyethylene with on top sterile

rubber gloves). If Amsidine-solution contacts the skin or the mucosa, the contact-place should be washed immediately and thoroughly with soap and water. After accidental contact with amsacrine during preparation acute systemic toxicity can occur (nausea, vomiting, headache, feeling of general maleise, urticaria).

Preparation of an intravenous solution
Amsidine is formulated as two sterile liquids that are aseptically combined prior to use. Each ampul contains 1.5 ml of amsacrine solution in N, N-dimethylacetamide (50 mg amsacrine per ml). Each vial contains L-lactic acid (42,9 mg) in water for injections (up to 15 ml). Exactly 1.5 ml of the solution from the ampul is removed by aid of a graduated glass syringe and immediately added to the vial with L-lactic acid (see section 6.2 incompatibilities). Mixe by thoroughly shaking. The resulting orange-red solution contains Amsidine 5 mg/ml.
Because of phlebitis that may occur at doses greater than 70 mg/m^2, Amsidine must be diluted in 500 ml 5 % glucose solution and infused over 60 to 90 minutes in PVC or polythene infusion bags and PVC administration sets.

Method of removal
Any unused product, any items that come into contact with the product and waste material must be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORIZATION NUMBER(S)

RVG 09084

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

May 12th 1982.

10. DATE OF REVISION OF THE TEXT

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Based on IPI of July 18th 2003.