LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Amsacrine NordMedica
(amsacrine)

SE/H/1383/01/DC

This module reflects the scientific discussion for the approval of Amsacrine NordMedica. The procedure was finalised on 2015-12-09. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

NordMedica A/S has applied for a marketing authorisation for Amsacrine NordMedica, 75 mg/1.5 ml, concentrate and solvent for concentrate for solution for infusion. The active substance is amsacrine.

For approved indications, see the Summary of Product Characteristics.

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83 and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

m-AMSA is a synthetic acridine derivative with cytostatic effect. The mechanism of action is not clarified in details but is ascribed to the ability of the substance to bind to DNA and Topo II, thereby inhibiting the synthesis of DNA and induce cell death. Amsacrine belongs to the pharmacotherapeutic group: Antineoplastic and immunomodulating agents, other antineoplastic agents with ATC code L01XX01.

Since Amsacrine NordMedica has been in clinical use for more than 10 years, the pharmacological effect of Amsacrine NordMedica has been proved in humans.

III.2 Pharmacokinetics

m-AMSA is extensively metabolised in the liver and the elimination is biphasic with a half-life of up to 6.5 hours in dogs. Excretion occurs to a high extent via the bile mainly as metabolites.

III.3 Toxicology

m-AMSA is known to produce its toxic effects mainly due to its myelosuppressive properties. Adverse effects seen after single dose administration are leukopenia, anaemia and increased serum activity of liver enzymes. Repeated administration also causes gastrointestinal and mucosal adverse effects in animals. Results from rats indicate that tissues with the highest rates of cell turnover are the main target organs for toxicity.

Because m-AMSA 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. Data from *in vitro* and *in vivo* studies indicates, that m-AMSA is slightly genotoxic in both non-human and human mammalian cells.

Carcinogenesis studies of m-AMSA in rats indicate an increased incidence of small intestinal adenocarcinomas and in female Wistar rats significantly increased incidences of mammary tumors. No human carcinogenic potential of m-AMSA has been identified in a large follow-up study of AML patients treated with m-AMSA combination therapy, and no significant excess of secondary malignancies has been reported.

m-AMSA 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 m-AMSA therapy and recommendation for contraception in both males and females.

III.4 Environmental Risk Assessment (ERA)

ERA has not been submitted by the Applicant, but instead a rationale was provided showing that environmental exposure to Amsacrine NordMedica would not increase based on the $PEC_{surface\ water}$ value being lower than the threshold level value 0.01 µg/L. This is considered acceptable.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

The pharmacokinetic information is extracted mainly from published literature from the 1980ies, and is briefly described in the clinical overview.

Absorption
Not applicable, administered intravenously.

Distribution
Plasma protein binding has been reported to be 97%, and independent of concentration in the range 1-100 μM. A study by Paxton et al (1986) suggested that a fraction of the binding could be covalent. Volume of distribution has been reported to 70-110 L/m2. Uptake into nucleated blast cells seems to be fast, with reported concentrations 5 times higher than peak plasma concentration (Linssen 1993). Concentrations in cerebrospinal fluid were low (0-2% of plasma concentrations) in published studies.

Elimination
A biphasic elimination of amsacrine has been reported with a fast distribution half-life (0.25-1.6 h) followed by an elimination half-life of 4.7-9 h. Urinary excretion of unchanged drug seems to be of limited importance (fe≈0.1) in patients with normal organ function. Metabolites are excreted both in urine and bile.

Metabolism
Metabolism has not been studied in humans. In mice and rats, most of a given amsacrine dose is excreted in the bile as 5´and 6´glutathione conjugates. An in vitro study in rat liver microsomes also found oxidative metabolites, which were considerably more cytotoxic than amsacrine itself (Shoemaker 1984).

There is a substantial lack of knowledge regarding the metabolic pathways, catalysing enzymes and transporters as well as metabolite activity and elimination in human. In the secondary round of assessment, the applicant provided further discussions about the metabolism of amsacrine. Given the remaining uncertainties regarding amsacrine elimination, a cautionary statement in the SmPC regarding coadministration of enzyme inhibitors and inducers is given.

Special populations
One study with radiolabelled amsacrine (Hall et al 1984) included 3 patients with impaired renal and 10 patients with impaired hepatic function. In the renally impaired patients, a lower fraction of the radiolabelled dose (2-16% instead of 35%) was found in the urine, and in 2 of the 3 renally impaired patients, the clearance was estimated to be lower than in the average subject with normal organ function (16 and 43%). Patients with severe liver dysfunction had a longer terminal half-life of amsacrine (17 h compared with 7 h) and a higher fraction of the dose excreted unchanged in urine (20% instead of 12%). Increased amsacrine toxicity has been reported in patients with impaired liver function (elevated bilirubin, Mahal et al 1981).

The limited pharmacokinetic data from patients with impaired hepatic function suggest an effect of hepatic impairment on the pharmacokinetics of amsacrine. The effect of renal impairment is expected to be smaller, given the small fraction of the dose that is excreted unchanged, but a lower amsacrine clearance compared with the average normal patient was seen in 2 of the 3 patients with renal impairment in the publication submitted. Nothing is

known about renal excretion of potentially toxic metabolites. A dose adjustment of 20-30% in moderate and severe renal and hepatic impairment is recommended in the SmPC, which is the recommendation previously established in Sweden. Effects of mild organ impairment seem unlikely, and a normal starting dose is recommended to these patients.

There is no available information on covariates such as gender, weight, race or age on amsacrine pharmacokinetics. Drug dosing is based on body surface area, aiming to compensate for the effect of size.

Interactions

Almost no in vitro or in vivo drug-drug interaction data for amsacrine is available in current literature. It is thus unknown both which enzymes and transporters that are responsible for amsacrine elimination as well as whether amsacrine can act as an inhibitor or inducer of drug metabolising enzymes or transporters. This lack of knowledge is communicated in the SmPC, and concomitant use of strong enzyme inhibitors or inducers should be avoided. Preclinical data on amsacrine as an inhibitor of the enzyme aldehyde oxidase is available, which would indicate a risk for interaction with methotrexate, but these data is of unknown clinical relevance.

IV.2 Clinical efficacy

Based on the bibliographical data provided by the Applicant and the current clinical use of amsacrine it was concluded that the product still had a place in therapy in the refractory / relapsed AML setting (with the exception of APL) as salvage therapy, in combination with e.g. cytarabine and etoposide (ACE) or fludarabine, cytarabine, G-CSF, m-AMSA (FLAG-m-AMSA).

IV.3 Clinical safety

After amendments the SmPC wording is considered to reflect the known safety profile of amsacrine.

IV.4 Risk Management Plans

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Amsacrine NordMedica.

Safety specification

Summary of safety concerns	
Important identified risks	Hematologic toxicity and bone-marrow suppression
	High susceptibility to infections
	Gastro-intestinal adverse drug reactions
	Hypersensitivity/ allergic reactions
	Cardiac toxicity
	Cytostatic extravasation
Important potential risks	Medication error
	Interactions with other drugs
	Lactation

Summary of safety concerns	
	Pregnancy
	Paediatric population
	Overdosing
	Reproductive system, congenital, familial and genetic disorders in patients in the reproductive age
	Patients with impaired liver and/or impaired renal function
Missing information	Elderly
	Porphyria

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of Safety Concerns and Planned Risk Minimisation Activities as proposed/ approved in RMP

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Hematologic toxicity and bone-marrow suppression.	Proposed text in SmPC and PIL and routine PhV activities. Other routine risk minimisation measures: - Prescription only medicine Use restricted to physicians experienced in the treatment of acute leukaemia.	None proposed
High susceptibility to infections	Proposed text in SmPC and PIL and routine PhV activities. Other routine risk minimisation measures: - Prescription only medicine Use restricted to physicians experienced in the treatment of acute leukaemia.	None proposed
Gastro-intestinal adverse drug reactions	Proposed text in SmPC and PIL and routine PhV activities. Other routine risk minimisation measures:	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	- Prescription only medicine Use restricted to physicians experienced in the treatment of acute leukaemia.	
Hypersensitivity/ allergic reaction	Proposed text in SmPC and PIL and routine PhV activities. Other routine risk minimisation measures: - Prescription only medicine Use restricted to physicians experienced in the treatment of acute leukaemia.	None proposed
Cardiac toxicity	Proposed text in SmPC and PIL and routine PhV activities. Other routine risk minimisation measures: - Prescription only medicine Use restricted to physicians experienced in the treatment of acute leukaemia.	None proposed
Cytostatic extravasation	Proposed text in SmPC and PIL and routine PhV activities. Other routine risk minimisation measures: - Prescription only medicine Use restricted to physicians experienced in the treatment of acute leukaemia.	None proposed
Medication error	Proposed text in SmPC and PIL and routine PhV activities. Other routine risk minimisation measures: - Prescription only medicine Use restricted to physicians experienced in the treatment of acute leukaemia.	None proposed
Interactions with other drugs	Proposed text in SmPC and PIL and routine PhV activities.	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Other routine risk minimisation measures: - Prescription only medicine Use restricted to physicians experienced in the treatment of acute leukaemia.	
Lactation	Proposed text in SmPC and PIL and routine PhV activities. Other routine risk minimisation measures: - Prescription only medicine Use restricted to physicians experienced in the treatment of acute leukaemia.	None proposed
Pregnancy	Proposed text in SmPC and PIL and routine PhV activities. Other routine risk minimisation measures: - Prescription only medicine Use restricted to physicians experienced in the treatment of acute leukaemia.	None proposed
Pediatric Population	Proposed text in SmPC and PIL and routine PhV activities. Other routine risk minimisation measures: - Prescription only medicine Use restricted to physicians experienced in the treatment of acute leukaemia.	None proposed
Overdosing	Proposed text in SmPC and PIL and routine PhV activities. Other routine risk minimisation measures: - Prescription only medicine Use restricted to physicians experienced in the treatment of acute leukaemia.	None proposed
Reproductive system, congenital, familial and	Proposed text in SmPC and PIL and routine PhV	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
genetic disorders in patients in the reproductive age	activities. Other routine risk minimisation measures: - Prescription only medicine Use restricted to physicians experienced in the treatment of acute leukaemia.	
Patients with impaired liver and/or impaired renal function	Proposed text in SmPC and PIL and routine PhV activities. Other routine risk minimisation measures: - Prescription only medicine Use restricted to physicians experienced in the treatment of acute leukaemia.	None proposed
Elderly	Proposed text in SmPC and PIL and routine PhV activities. Other routine risk minimisation measures: - Prescription only medicine Use restricted to physicians experienced in the treatment of acute leukaemia.	None proposed
Porphyria	Proposed text in SmPC and PIL and routine PhV activities. Other routine risk minimisation measures: - Prescription only medicine Use restricted to physicians experienced in the treatment of acute leukaemia.	None proposed

Summary of the RMP

The RMP is approved.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was Danish.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The use of amsacrine is considered well-established and the amended wording of the indication (amsacrine is indicated as salvage therapy of refractory/relapsed AML in adults, in combination with other chemotherapeutic agents) is considered reasonably justified and continues to have the support of the RMS.

The combination treatment upon failure constitutes an option in at least the Swedish national guideline for AML, but it is worth mentioning that this praxis is supported by literature.

The treating physician should consider the B/R of the proposed regimen in the individual patient and carefully monitor therapy as recommended in the SmPC.

The benefit/risk is considered positive.

List of recommendations not falling under Article 21a/22 of Directive 2001/83 in case of a positive benefit risk assessment

Area[1]	**Description**
Quality	The variation to implement terminal sterilization as a process step for the lactic acid solvent will be submitted in Q2 2016.

1. Areas: Quality, Non-clinical, Clinical, Pharmacovigilance

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The Decentralised procedure for Amsacrine NordMedica, 75 mg/1.5 ml, concentrate and solvent for concentrate for solution for infusion was positively finalised on 2015-12-09.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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