LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Amsalyo
(amsacrine)

SE/H/1668/01/DC
2017-0384

This module reflects the scientific discussion for the approval of Amsalyo. The procedure was finalised on 2018-04-26. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Eurocept International B.V. has applied for a marketing authorisation for Amsalyo, 75 mg, powder for concentrate for solution for infusion. The active substance is amsacrine.

Amsacrine (L01XX01) was developed in 1974, approved in Sweden in 1983 and used well beyond 10 years in the EU. Amsacrine is a synthetic aminoacridine derivative whose mechanism of action is still not fully understood, but includes DNA intercalation and DNA topoisomerase 2-alpha inhibition.

For approved indications, see the Summary of Product Characteristics.

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

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83/EC 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

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.

The Applicant has provided adequate information on the pharmacological properties of m-AMSA. Conventional safety pharmacology studies have not been performed. This is acceptable, considering the long clinical experience.

Pharmacokinetics
The Applicant has provided adequate information on pharmacokinetic properties of m-AMSA in mice, rats, rabbits and dogs.

Toxicology
The Applicant has provided relevant published literature on toxicology of m-AMSA, where it is presented that toxic effects of m-AMSA are mainly due to myelosuppressive properties. m-AMSA interferes with DNA and has therefore genotoxic and cytotoxic properties, and is categorized as class 2B human carcinogen by WHO and IARC. In the rat carcinogenicity study an increased incidence of small intestinal adenocarcinomas has been seen and in females significantly increased incidences of mammary tumors. m-AMSA is considered embryotoxic, fetotoxic and teratogenic in rats.

The text in the SmPC sections 4.6 and 5.3 is adequate and identical to that agreed in a previous procedure for Amekrin (SE/H/1383/01/DC).

Environmental Risk Assessment (ERA)
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of amsacrine released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

A calculation of a PECsw based on the prevalence of leukemia results in a value below 0.01 µg/L. Experimental Log Kow of amsacrine is 2.85 at pH 7.4

It is agreed that no further ERA studies are needed.

IV. CLINICAL ASPECTS

IV.1 Introduction

The clinical parts of the application for Amsalyo are based solely on bibliographical data.

IV.2 Pharmacokinetics

The pharmacokinetic information is extracted mainly from published literature from the 1980ies.Most published studies present data from formulations based on amsacrine concentrate. As the current lyophilised formulation results in a solution with the same active substance and concentration as other amsacrine products, and does not contain excipients that

are expected to affect the disposition of the drug substance, published pharmacokinetics data is considered applicable to the new formulation.

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).

The lack of knowledge about the main metabolic pathways as well as responsible catalysing enzymes and transporters makes it difficult to address the risk for drug-drug interactions with other medicinal products that may increase or decrease amsacrine exposure. This deficit is acceptably described in the SmPC section 5.2 and 4.5.

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 suggests an effect of hepatic impairment on the pharmacokinetics of amsacrine, and a starting dose adjustment is proposed in patients with moderate or severe hepatic impairment. 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 in moderate and severe renal impairment is also proposed. Based on the limited data available, the proposed recommendations are acceptable.

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. Lack of data on gender and race could be acceptable, as no larger effects are expected.

Interactions

No in vitro or in vivo drug-drug interaction data are presented. It is unknown 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 problem is acceptably described in the SmPC section 4.5, where it states that other medicinal products should be used with caution together with amsacrine, and that concomitant use of strong enzyme inhibitors or inducers should be avoided.

IV.3 Pharmacodynamics

Although the mechanism of action is not fully characterised, m-AMSA induces DNA intercalation of the three coplanar rings and Topo II (Type II Topoisomerase) inhibition with production of DNA double-strand breaks occurring at base sequences different from those of anthracyclines and Etoposide (VP-16). The provided description of the pharmacodynamic effects is considered adequate.

IV.4 Clinical efficacy

The provided documentation sufficiently supports WEU of amsacrine as salvage therapy of refractory/relapsed AML in adults, in combination with other chemotherapeutic agents.

IV.5 Clinical safety

Amsacrine has been used for decades within the EU and the drug's safety profile must be considered well known. The provided documentation sufficiently describes the safety profile for amsacrine.

IV.6 Risk Management Plans

The MAH has submitted an updated risk management plan version 1.2 (dated 5 March 2018), 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 Amsalyo.

Safety specification

Summary table of safety concerns as proposed in the RMP

Important identified risks	-
Important potential risks	Interaction with drugs
	Embryo-foetal toxicity and teratogenicity
	Impaired fertility
Missing information	-

The proposed safety concerns are acceptable.

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 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 Dutch.
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

Amsacrine has been used for decades within the EU. The provided documentation sufficiently supports WEU of amsacrine as salvage therapy of refractory/relapsed AML in adults, in combination with other chemotherapeutic agents. This is also supported by the Swedish national guideline on AML. In the response to the LoI the Applicant has revised the SmPC 4.1 accordingly.

The safety profile of amsacrine must be considered well known and includes myelosuppression and cardiac toxicity. The provided safety documentation is considered sufficient.

The benefit/risk ratio is considered positive and Amsalyo, 75 mg, powder for concentrate for solution for infusion is recommended for approval.

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

N/A

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

N/A

VII. APPROVAL

The Decentralised procedure for Amsalyo, 75 mg, powder for concentrate for solution for infusion was positively finalised on 2018-04-26.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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