Drug Monograph

A - Drug Name

amsacrine

SYNONYM(S): acridinyl anisidide; AMSA; m-AMSA

COMMON TRADE NAME(S): AMSA P D® (Erfa)

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B - Mechanism of Action and Pharmacokinetics

Amsacrine is an acridine dye derivative. The mechanism of action is incompletely defined but amsacrine appears to be a DNA intercalator. It causes double-strand breaks in DNA, and inhibits topoisomerase II, leading to S phase and G2 arrest. Cytotoxicity is greatest when cells are cycling.

Absorption	Oral: yes (poorly absorbed)	
Distribution	To all tissues except the brain. High initial concentrations in liver, spleen and kidney.	
	Cross blood brain barrier?	Trace
	Volume of distribution	1.67 L/kg; 87.1 L/m^2
	PPB	97%
Metabolism	Pharmacokinetics are dose dependent. Amsacrine is metabolized extensively in the liver to amsacrine-glutathione conjugate	
	Active metabolites	None known
	Inactive metabolites	Yes, in bile
Elimination	Primarily excreted in bile; about 80% in feces within 48 hours.	
	Urine	35% within 72 hours; 20% as intact drug
	Half-life	t ½ α: 10-15 minutes

t ½ ß: 8-9 hours

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C - Indications and Status

Health Canada Approvals:

- Induction of remission in acute adult leukemia refractory to conventional treatment

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D - Adverse Effects

Emetogenic potential: Low

Extravasation Potential: Vesicant

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arrhythmia (rare, increased with hypokalemia)	I
	Cardiomyopathy (rare)	E
	Heart failure (rare)	E
	Hypotension	E
Dermatological	Alopecia	E
	Rash	E
	Urticaria	E
Gastrointestinal	Anorexia	E
	Diarrhea (up to 17%)	E
	GI hemorrhage	E
	Nausea, vomiting (up to 30%)	I
	Weight changes	E
	Abdominal pain (>10%)	E
	Mucositis (30%)	E
General	Fatigue	E
Hematological	Hemorrhage	E
	Myelosuppression (100%) (nadir 11-13 days, recovery 17-25 days)	E
Hypersensitivity	Allergic reaction (rare, type 1 anaphylactoid)	I

Infection	Sepsis (and fever)		E	
Injection site	Phlebitis (chemical)	I		
Metabolic / Endocrine	Hyperuricemia (tumour lysis)	I		
Musculoskeletal	Myalgia		E	
Nervous System	Confusion		E	
	Dizziness		E	
	Headache		E	
	Paresthesia		E	
	Seizure (rare)		E	
Renal	Renal failure (rare)		E	
	Proteinuria		E	
Reproductive and breast disorders	Infertility			L
Respiratory	Dyspnea		E	
Urinary	Hematuria		E	
	Urine discoloration (orange)		E	
Hepatobiliary	↑ LFTs (may be severe)		E	

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.
Dose-limiting side effects are underlined.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The major side effects are **myelosuppression** and **stomatitis**. Myelosuppression has a rapid onset and usually persists for 3 weeks after administration.

The **tissue necrosis** that occurs with **extravasation** may occur weeks to months after the treatment. Patients must be observed for delayed reactions and prior injection sites carefully inspected.

Hyperuricemia during periods of active cell lysis can be minimized with allopurinol and hydration. In hospitalized patients the urine may be alkalinized, by addition of sodium bicarbonate to the IV fluids, if tumour lysis is expected.

Cardiotoxicity is unusual, although arrhythmias (including QT prolongation) have been documented and occur in about 1% of patients who have not received prior chemotherapy. It does not appear to be dose-dependent. Thirty percent of patients experiencing arrhythmias had hypokalemia. Patients who have had underlying cardiac disease, had received prior mediastinal radiation or had previous exposure to anthracyclines may be at increased risk for cardiotoxicity. The manufacturer recommends monitoring of cardiac rhythm during and after drug administration.

Phlebitis can be reduced by infusing the diluted drug over a period of 60-120 minutes, or by

giving it through a central venous line.

Type I **hypersensitivity** reactions have been reported with rash, pruritus and erythema on the first dose of amsacrine. No hypotension was reported. Rashes have also been reported among laboratory personnel who handle bulk drugs suggesting a Type IV skin-sensitizing process.

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E - Dosing

Guidelines for dosing include consideration of white blood cell count. Dosage may be reduced and/or delayed in patients with bone marrow depression due to cytotoxic/radiation therapy as well as with renal or hepatic insufficiency.

Adults:

Induction:
Intravenous: 75-125mg/m² Daily x 5 days

- *Two courses may be necessary to achieve induction.* The second course should not be administered until recovery of myelosuppression, unless marrow infiltration is persistent. Increase by 20% in the second and each subsequent course if no significant toxicity in the preceding course, and if marrow hypoplasia has not been achieved

Maintenance:

- 50% of induction dose depending on peripheral blood counts every 4-8 weeks

Dosage with Toxicity:

Myelosuppression:

- Decrease dose by 20% if patient has had life-threatening infection or hemorrhage during the previous course.

Dosage with Hepatic Impairment:

Bilirubin	*OR*	*AST*	*% usual dose*
1-2.5x ULN		2-5x ULN	50%
>2.5 x ULN		>5x ULN	reduce further or omit

Dosage with Renal Impairment:

Creatinine Clearance (mL/min)	% Usual Dose
40-60	60-75%
<40	OMIT

Dosage in the elderly:

Safety and efficacy have not been established. Elimination may be slower in the elderly.

Children:

Safety and effectiveness have not been established.

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F - Administration Guidelines

- Dilute only with supplied lactic acid diluent.
- May use glass syringe to withdraw drug from the ampoule to the vial. If a plastic syringe is used, the drug should not remain in the syringe for more than 15 minutes.
- Dilute further in 500mL bag of Dextrose 5%. Do not dilute with Normal Saline.
- For IV infusion only. Infuse over 60-90 minutes.
- Incompatible with any solution containing chloride ions

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G - Special Precautions

Contraindications:

- in patients who are hypersensitive to amsacrine or to acridine derivatives (e.g., acriflavine), or to any ingredients in the formulation.
- in patients who have pre-existing drug-induced or radiotherapy-induced bone marrow suppression.

Warnings/Precautions:

- Avoid concomitant use of live vaccines.
- The risk of arrhythmia may be increased in hypokalemia, concomitant use of diuretics, other nephrotoxic drugs or previous anthracycline treatment.
- Fluid or electrolyte imbalance should be corrected before starting amsacrine. Ensure serum potassium level is normal immediately before and during amsacrine infusion.

Other Drug Properties:

- Carcinogenicity: Probable

Pregnancy and Lactation:

- Clastogenicity: Yes
- Mutagenicity: Yes
- Fetotoxicity: Yes
- Teratogenicity: Yes
  Amsacrine's safe use in pregnancy has not been established. Adequate contraception should be used by both sexes, during treatment and for at least 6 months after the last dose. Men should also be advised not to father a child during treatment.
- Fertility effects: Probable
- Breastfeeding:
  Not recommended due to the potential secretion into breast milk.

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H - Interactions

Insufficient data are available to prove or disprove interactions.

Amsacrine is highly protein bound and the potential exists for interactions when co-administering

other highly protein bound drugs.

Avoid the concomitant administration of live vaccines.

Amsacrine does not appear to increase the risk of doxorubicin-induced cardiac toxicity.

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I - Recommended Clinical Monitoring

Recommended Clinical Monitoring

- Liver function tests; baseline and regular
- Renal function tests (including uric acid and electrolytes); baseline and regular
- CBC; baseline and frequent
- Cardiac rhythm; during and after administration
- Clinical monitoring for infection, bleeding, mucositis, diarrhea, nausea/vomiting, infusion site reactions; regular
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - References

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