DRUG NAME: Amsacrine

SYNONYM(S): m-AMSA,[1] amsidyl[2]

COMMON TRADE NAME(S): AMSA PD®

CLASSIFICATION: miscellaneous

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Although its mechanism of action is incompletely defined, amsacrine inhibits DNA synthesis by binding to and intercalating with DNA. Amsacrine also inhibits topoisomerase II activity[3,4] and may exert an effect on cell membranes.[2,5] This agent also possesses immunosuppressive and antiviral properties.[3] While amsacrine is not cell cycle phase-specific,[3,6] cytotoxicity is maximal during the G2 and S phases.[3,5]

PHARMACOKINETICS:

Oral Absorption	poor[5]	
Distribution	high levels achieved in gallbladder and kidneys; lower levels in lung, testes, muscle, fat, spleen, bladder, pancreas, colon, prostate, brain, and CSF[2]	
	cross blood brain barrier?[4]	minimal
	volume of distribution[1]	1.67 L/kg
	plasma protein binding[4]	96-98%
Metabolism	hepatic[4]	
	active metabolite(s)	no information found
	inactive metabolite(s)[4]	yes; including 5'-glutathione conjugate
Excretion	primarily biliary[2,5]	
	urine[2-4]	35%; 2-20% unchanged
	feces[2]	~80%
	terminal half life[4]	5-8 h; severe hepatic dysfunction[2]: 17 h
	clearance[7]	150 mL/min/m^2
Children	longer half life,[8] ~18 h	

Adapted from standard reference[3] unless specified otherwise.

USES:

Primary uses:
*Leukemia, acute

Other uses:

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Contraindications:
- history of hypersensitivity reaction to amsacrine or acridine derivatives (e.g., acriflavine)[3]
- pre-existing drug-induced or radiotherapy-induced bone marrow suppression[3]

Caution:

- dose reduce with significant hepatic dysfunction (bilirubin >34 umol/L) or renal impairment (BUN >7 mmol/L or serum creatinine >106 umol/L)[3]; see **Dosage Guidelines**
- monitor cardiac rhythm during and after drug administration[3]
- correct fluid or electrolyte imbalances, including serum potassium, prior to administration[3]
- in patients who have received high cumulative doses of anthracyclines[4]; amsacrine is not contraindicated in patients who have received previous treatment with anthracyclines[3]
- safety and efficacy in the elderly have not been established[3]

Carcinogenicity: carcinogenic in rats[9]

Mutagenicity: Mutagenic in mammalian *in vitro* mutation test.[9] Amsacrine is clastogenic in mammalian *in vitro* chromosome tests.[9]

Fertility: reversible decreased sperm production[4] and motility reported[1]; reproductive studies in animals not performed to date[3]

Pregnancy: The risks of amsacrine in pregnancy are undetermined. The drug is cytotoxic, therefore, the risks may be substantial.[3,10] No human studies of pregnancy outcomes after exposure have been published to date and there have been no reports of outcomes following inadvertent exposure during pregnancy. Amsacrine given intraperitoneally to rats resulted in decreased fetal weight and eye and jaw malformations.[1]

Breastfeeding is not recommended due to the potential secretion into breast milk.[1]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[11]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
allergy/immunology	allergic reaction (0.4%)[4]; some patients have been able continue therapy with antihistamine or corticosteroid pretreatment[2]
blood/bone marrow/ febrile neutropenia	***myelosuppression***; dose-limiting; prolonged bone marrow aplasia has occurred
	anemia (1-10%)[4]; mild to severe
	leukopenia; nadir days 11-13, recovery by days 17-25; granulocytopenia
	thrombocytopenia; mild to moderate; nadir days 12-14, recovery[1,4] by days 21-25
cardiovascular (arrhythmia)	arrhythmia (<1%); including acute and ventricular arrhythmia, atrial fibrillation, tachycardia, sinus tachycardia, and bradycardia; typically occurs during or immediately following infusion; several patients had received prior anthracycline therapy or were hypokalemic
	ECG changes
cardiovascular (general)	cardiomyopathy; typically occurs days to weeks following therapy[12]
	congestive heart failure; typically occurs in patients who had been pre-treated with anthracyclines
	decreased ejection fraction
	hypotension

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
constitutional symptoms	fatigue
	fever; unrelated to sepsis
	weigh gain/loss
dermatology/skin	*extravasation hazard: vesicant*[13]
	alopecia (≤100%)[11]; dose-related[6,14]
	injection site reactions including: irritation, necrosis, inflammation, and cutaneous inflammatory reaction
	rash; including purpuric and maculopapular
	urticaria
gastrointestinal	*emetogenic potential: low*[15]
	anorexia
	diarrhea (≤30%)[3,4]
	dysphagia
	gingivitis
	nausea and vomiting[3,4] (≤30%)[3,4]; typically mild to moderate[5]; not dose-related[6]
	mucositis/stomatitis (≤32%)[3,4]; dose-limiting[3,4]
	perirectal abscess (>10%)
hemorrhage	gum hemmorhage
	hematemesis
	hematuria
	hemorrhage, not otherwise specified
	purpura
hepatobiliary/pancreas	hepatic insufficiency, hepatitis, hepatic failure; deaths have occurred
infection	infections, not otherwise specified
metabolic/laboratory	elevated alkaline phosphatase and AST (10%)[4]
	elevated bilirubin (30%)[4]; typically transient
	elevated BUN
	elevated creatinine
	hyperuricemia
	hypomagnesemia[1]
	proteinuria
neurology	confusion (1-10%)[4]
	dizziness (1-10%)[4]
	emotional lability
	paresthesia (1-10%)[4]; hypoesthesia
	seizure (1-10%)[4]; typically occur in patients who have metabolic conditions

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
ocular/visual	blurred vision[4] (1-10%)[4]
pain	abdominal pain (>10%)
	headache (1-10%)[4]
	musculoskeletal pain
pulmonary	dyspnea
renal/genitourinary	orange-red discolouration of urine[4] (>10%)[4]
	renal failure
sexual/reproductive function	decreased sperm production[4] and motility[1] (<1%)[4]; reversible[1]
vascular	phlebitis (>10%)[4]; concentration-related; incidence is reduced by infusing over at least 60 minutes

Adapted from standard reference[3] unless specified otherwise.

Cardiotoxicity: Similar to the anthracyclines, both acute (arrhythmia) and chronic (cardiomyopathy) cardiac toxicities have been reported.[12] These toxicities are rare, occurring in 1-2% of patients who have not received prior chemotherapy.[2,12] Though amsacrine should be used with caution in patients who have received high cumulative doses of anthracyclines,[4] it does not potentiate the increased risk of doxorubicin-induced cardiac toxicity[3] and is not contraindicated in patients who have received previous treatment with anthracyclines.[3]

The exact mechanism by which amsacrine causes arrhythmias is unknown,[14] though QT interval prolongation does occur.[6] Hypokalemia, which also causes QT prolongation, may contribute to the risk of developing arrhythmias.[3,6] This risk may be minimized by ensuring a normal serum potassium level immediately prior to and during amsacrine administration.[3] As arrhythmias typically occur during or immediately following infusion, monitor cardiac rhythm during and after drug administration.[3] Fluid imbalance should also be corrected prior to amsacrine administration.[3] Patients with arrhythmias may receive amsacrine with careful monitoring and correction of electrolyte abnormalities.[2]

Unlike the anthracyclines, the risk of acute congestive heart failure is not related to cumulative dose.[12]

Hyperuricemia may result from cell lysis by cytotoxic chemotherapy and may lead to electrolyte disturbances or acute renal failure.[16] It is most likely with highly proliferative tumours of massive burden, such as leukemias, high-grade lymphomas, and myeloproliferative diseases. The risk may be increased in patients with preexisting renal dysfunction, especially ureteral obstruction. Suggested prophylactic treatment for high-risk patients[17]:

- aggressive hydration: 3 L/m²/24 hr with target urine output >100 ml/h
- if possible, discontinue drugs that cause hyperuricemia (e.g., thiazide diuretics) or acidic urine (e.g., salicylates)
- monitor electrolytes, calcium, phosphate, renal function, LDH, and uric acid q6h x 24-48 hours
- replace electrolytes as required
- allopurinol 600 mg po initially, then 300 mg po q6h x6 doses, then 300 mg po daily x 5-7 days

Urine should be alkalinized only if the uric acid level is elevated, using sodium bicarbonate IV or PO titrated to maintain urine pH>7. Rasburicase (FASTURTEC®) is a novel uricolytic agent that catalyzes the oxidation of uric acid to a water-soluble metabolite, removing the need for alkalinization of the urine.[18] It may be used for treatment or prophylaxis of hyperuricemia; however, its place in therapy has not yet been established. Aluminium hydroxide (AMPHOGEL®) may be added orally if phosphate becomes elevated. If aluminium hydroxide has been added, discontinue sodium bicarbonate.[19]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
doxorubicin[3]	no increased risk of doxorubicin-induced cardiotoxicity		

Highly protein bound drugs may displace amsacrine from albumin resulting in increased free amsacrine levels and toxicity.[3]

SUPPLY AND STORAGE:

***Injection*:** Erfa Canada Inc. supplies 75 mg preservative-free ampoules of amsacrine in N,N-dimethylacetamide solvent. 13.5 mL of preservative-free L-lactic acid diluent also supplied. Store at room temperature.[3]

For basic information on the current brand used at the BC Cancer Agency, see Chemotherapy Preparation and Stability Chart in Appendix.

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at the BC Cancer Agency, see Chemotherapy Preparation and Stability Chart in Appendix.
Additional information:

- Dilute only with supplied L-lactic acid diluent.[3]
- Amsacrine forms an immediate precipitate in the presence of chloride ions; do not dilute with saline solutions or solutions containing chloride ions or mix with drugs that are chloride or hydrochloride salts.[3,4] Catheters flushed with heparin/saline solutions should be rinsed with D5W before administering amsacrine.[1]
- Use of glass syringes and avoidance of plastic filters to draw up undiluted amsacrine solutions is recommended as the N,N-dimethylacetamide solvent has been reported to dissolve plastic syringes and filters. Plastic syringes can be used, providing that amsacrine remains in the syringes for no longer than 15 minutes.[3] The solution can be placed in plastic bags when diluted for IV infusion.[3,4]

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

BCCA administration guideline noted in ***bold***, ***italics***

Subcutaneous[3]	not used due to corrosive nature
Intramuscular[3]	not used due to corrosive nature
Direct intravenous[3]	not used due to corrosive nature
Intermittent infusion[3]	***over 60-90 minutes***
Continuous infusion	has been used but not recommended[1,4] (more toxic than intermittent infusion)[1]
Intraperitoneal[3]	not used due to corrosive nature
Intrapleural[3]	not used due to corrosive nature
Intrathecal[3]	not used due to corrosive nature
Intra-arterial[3]	not used due to corrosive nature
Intravesical	no information found

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

***Adults*:**

BCCA usual dose noted in ***bold, italics***

Intravenous:	Cycle Length: 3-4 weeks, induction[3]:	75-125 mg/m^2 IV once daily for 5 consecutive days starting on day 1 (total dose per cycle 375-625 mg/m^2) • dose should be increased by 20% in the second and each subsequent cycle if marrow hypoplasia has not been achieved and the patient has had no significant toxicity in the preceding cycle
	4-8 weeks, maintenance[3]:	approximately half of the induction dose • dependant on blood counts
Concurrent radiation:	limited experience, avoid combination[11]	
Dosage in myelosuppression:	modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix 6 "Dosage Modification for Myelosuppression"	
Dosage in renal failure:	dose reduction recommended[3]; the following guidelines have been used: BUN >7 mmol/L or serum creatinine >106 umol/L: give 70-75% of normal dose[1,2]	
Dosage in hepatic failure:	dose reduction recommended[3]; the following guidelines have been used: bilirubin >34 umol/L: give 70-75% of normal dose[1,2,4]	
Dosage in dialysis:	no information found	

Children:

has been used[1,4]

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