DRUG NAME: AMIFOSTINE

SYNONYM(S): Ethiofos, WR2721, ethanethiol, gammaphos, NSC-296961

COMMON TRADE NAME(S): ETHYOL®

CLASSIFICATION: cytoprotectant

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

MECHANISM OF ACTION:

Amifostine is a pro-drug which is activated to the free thiol metabolite at the tissue site. The thiol metabolite is responsible for most of the cytoprotective and radioprotective properties of amifostine. It is readily taken up by cells where it binds to and detoxifies reactive metabolites of platinum and alkylating agents as well as scavenges free radicals. Other possible effects include inhibition of apoptosis, alteration of gene expression and modification of enzyme activity.[1] Healthy cells are preferentially protected because amifostine and metabolites are present in healthy cells at 100-fold greater concentrations than in tumour cells.[1-3]

PHARMACOKINETICS:

Interpatient Variability	no information found	
Oral Absorption	not orally absorbed[4]	
Distribution	widely distributed throughout body[5] (highest: kidney, salivary gland, intestinal mucosa, liver, lung; lowest: brain, skeletal muscle)[6]	
	cross blood brain barrier? [6]	No
	volume of distribution[1]	7.4-8.7 L
	plasma protein binding[4,7]	4%
Metabolism	dephosphorylated by alkaline phosphatase in tissues primarily to WR-1065[2]	
	active metabolite	thiol (WR-1065)[2,3]
	inactive metabolite	disulfide (WR-33278)[2,3]
Excretion	non-linear elimination via rapid metabolism and tissue uptake[1]	
	urine	amifostine (0.7%), thiol (2.6%), disulfide (2.2%)[4]
	terminal half life[1]	amifostine 8 min, thiol 7.3 h
	clearance[2,3]	126-258 L/h
Gender	no information found	
Elderly	no information found	
Children	no information found	
Ethnicity	no information found	

USES:

Primary uses:
Chemoprotective agent[1,8-20]
Radioprotective agent[21-32]

Other uses:
Myelodysplastic syndrome[1]

*Health Canada Therapeutic Products Programme approved indication

SPECIAL PRECAUTIONS:

Contraindicated in patients with hypersensitivity reaction to aminothiols. Due to its potential to cause nausea, vomiting and hypotension, amifostine should be used cautiously in patients with cardiovascular conditions, cerebrovascular disease, dehydration, preexisting hypotension or predisposition to hypocalcemia.[2]

Use with curative chemotherapy: Animal data suggest that amifostine may interfere with antitumorigenic effects of chemotherapy and amifostine is not recommended with curative chemotherapy outside of a clinical trial. Interference has not been seen in human studies of amifostine thus far.[2,3]

Carcinogenicity: no information found.

Mutagenicity: Amifostine was not mutagenic in Ames test or clastogenic in mammalian *in vitro* chromosome test. Thiol metabolite (WR-1065) was mutagenic in Ames test and in mammalian *in vitro* mutation test but not clastogenic in mammalian chromosome tests.[2]

Fertility: no information found.

Pregnancy: FDA Pregnancy Category C. Studies in animals have revealed adverse effects on the fetus and there are no controlled studies in women. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.[2]

Breast feeding is not recommended due to the potential secretion into breast milk.[2]

SIDE EFFECTS:

ORGAN SITE	SIDE EFFECT	ONSET			
Dose-limiting side effects are in ***bold, italics*** I = immediate (onset in hours to days); E = early (days to weeks); D = delayed (weeks to months); L = late (months to years)					
allergy/immunology	allergic reactions (3-5%)[4]	I			
	sneezing (17-35%)	I			
cardiovascular (general)	***hypotension*** (67%, symptomatic 3-15%)[1,4,22,24,26]	I			
constitutional symptoms	fatigue (10%)[4]		E		
	feeling of coldness (rare)[7,19]		E		
	feeling unusually warm or flushed (rare)[7,19]	I			
	sneezing (17%)[7]		E		
dermatology/skin	*extravasation hazard*: none				
	mild rash (rare)[1]	I			
gastrointestinal	*emetogenic potential*: variable alone: moderate (3-7%)[1] with chemotherapy: moderate-high (70-90%)[1] with radiotherapy: low-moderate (40%, severe 3-5%)[1,4]	I			
	hiccups (rare)	I			
metabolic/laboratory	hypocalcemia (rare)[33]	I			

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neurology	dizziness (5%)[4]	I			
	somnolence (13%)	I			

Adapted from reference[2] unless specified otherwise.

Hypotension is usually asymptomatic but rarely causes dizziness or fainting. It may be associated with dyspnea, apnea, hypoxia, and rarely, seizures, loss of consciousness, respiratory arrest or renal failure.[2,3] It commonly occurs 14 minutes after the start of the infusion and lasts for 5-15 minutes. Hypotension is mediated by the active thiol metabolite, probably due to direct relaxation of vascular smooth muscle.[19] Patients should be adequately hydrated prior to amifostine infusion. Consider holding antihypertensives for 24 hours prior to amifostine infusion.[1]

- *for patients treated with amifostine 200 mg/m^2 dose for radiation-induced xerostomia*, blood pressure should be monitored at least before and immediately after the infusion, and thereafter as clinically indicated.[34]
- *for patients treated with amifostine 910 mg/m^2 dose for cytotoxic chemoprotection*, blood pressure should be monitored every 5 minutes during the infusion, and thereafter as clinically indicated. Patients should be kept in a supine position during the infusion.[34] Patients with symptomatic or significant reduction in systolic blood pressure (see table below) should have their infusion interrupted and managed symptomatically[2,5,34]

	Baseline Systolic Blood Pressure (mm Hg)				
	< 100	**100-119**	**120-139**	**140-179**	**≥ 180**
Decrease in systolic blood pressure during infusion	≥ 20	≥ 25	≥ 30	≥ 40	≥ 50

If the blood pressure returns to normal within 5 minutes and the patient is asymptomatic, the infusion may be restarted so that the full dose of amifostine may be given. If the full dose cannot be given, the dose for subsequent cycles should be reduced to 740 mg/m^2.

Hypocalcemia may occur transiently but is rarely clinically significant.[1,33] Tetany secondary to hypocalcemia has been reported in one patient.[33] Onset of hypocalcemia seems to be about four hours after the amifostine infusion.[33,35]Hypocalcemia may be due to inhibition of parathyroid hormone (PTH) excretion and enhanced calciuria.[19,33] Calcium levels may return to normal within a week without further treatment.[35] Serum calcium should be monitored in patients at risk for hypocalcemia (eg, nephrotic syndrome, multiple doses of amifostine).[1,33] If clinically significant hypocalcemia occurs, calcium supplements should be considered.[1,2] In one patient with documented reduced PTH levels, calcium carbonate and calcitriol orally were given for 24 hours before amifostine therapy.[33]

Nausea and Vomiting: Prophylactic antiemetics were used in most clinical trials (usually serotonin antagonists)[22,26] and the manufacturer recommends low dose serotonin receptor antagonist 1-2 hours prior to amifostine.[36]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
anthracyclines (doxorubicin, epirubicin)[1]	small increase in anthracyclines AUC	unknown	no adjustments needed
docetaxel[1]	no alteration of pharmacokinetics		no adjustments needed

AGENT	EFFECT	MECHANISM	MANAGEMENT
fluorouracil[37]	no alteration of pharmacokinetics		no adjustments needed
mitomycin[1,7]	no alteration of pharmacokinetics		no adjustments needed
paclitaxel[1]	small decrease in paclitaxel AUC	unknown	no adjustments needed
platinum agents (carboplatin,[17,38-40] cisplatin[41]	moderate reduction in carboplatin and cisplatin elimination	reduced renal clearance of carboplatin and cisplatin	monitor for possible increase in carboplatin and cisplatin toxicity during concomitant use in patients with renal dysfunction[17]
topotecan	no effect on topotecan pharmacokinetics[42]		no adjustments needed

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on solution preparation and compatibility, see Chemotherapy Chart in Appendix.

Injection: 500mg single-dose vial containing sterile, lyophilized powder of amifostine (anhydrous). Store at room temperature.[2]

Reconstitute powder with 9.7 mL NS to give final concentration of 50 mg/mL.[2]

***Reconstituted solution for injection*:** Reconstituted solution is stable for up to 5 hours at room temperature and for up to 24 hours in the refrigerator.[2]

***Diluted solution for infusion*:** Solution should be further diluted with NS to a final concentration of 5-40 mg/mL. Diluted solution is stable for up to 5 hours at room temperature and up to 24 hours in refrigerator.[2]

Compatibility: The following *chemotherapy agents* are compatible via Y-site: bleomycin, carboplatin, carmustine, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, docetaxel, doxorubicin, etoposide, fludarabine, fluorouracil, gemcitabine, ifosfamide, methotrexate, mitomycin, mitoxantrone, vinblastine, and vincristine.[43]

The following *non-chemotherapy agents* are compatible via Y-site: calcium gluconate, cimetidine, diphenhydramine, dopamine, dobutamine, furosemide, granisetron, heparin, hydrocortisone sodium phosphate, hydrocortisone sodium succinate, leucovorin, lorazepam, magnesium sulfate, mannitol, mesna, methylprednisolone, metoclopramide, morphine sulfate, ondansetron, potassium chloride, promethazine, ranitidine, sodium bicarbonate.[43]

Incompatibility: The following are incompatible via Y-site: chlorpromazine, cisplatin, hydroxyzine, prochlorperazine.[43]

PARENTERAL ADMINISTRATION:

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

Subcutaneous	investigational[44]
Intramuscular	no information found
Direct intravenous	no information found

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

Intermittent infusion	***for radioprotection, infuse over 3 min, 15-30 min prior to radiation***
	for chemoprotection, infuse over 15 min, initiated 30 min prior to chemotherapy; longer infusions not well tolerated.
Continuous infusion	no information found
Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	no information found
Intra-arterial	no information found
Intrarectal (topical)	investigational[45]
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.

Adults:

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

Intravenous:	For cytotoxic chemoprotection	500-910 mg/m^2 IV once daily started 30 min before chemotherapy.[2,3,11,14,46] For patients receiving 910 mg/m^2 who experience hypotension which does not resolve quickly, the amifostine dose[2,3,34] for subsequent courses should be reduced to 740 mg/m^2.
	For prevention of radiation-induced xerostomia	***200* mg/m^2** (range 200-340 mg/m^2) ***IV once daily, beginning 15-30 min prior to radiation therapy***.[22,23,26] Blood pressure should be monitored immediately before and after the infusion.[2,3,47]
Duration of therapy:		no information found
Concurrent radiation:		protection of radiation-induced xerostomia
Dosage in myelosuppression:	no adjustment required	
Dosage in renal failure:	no information found	
Dosage in hepatic failure:	no information found	
Dosage in dialysis	no information found	

Children:

Doses similar to those for adults have been used. However, the safety, efficacy and dosage have not been established.[2]

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