7. Hypocalcemia
Serum calcium levels should be monitored in patients at risk of hypocalcemia, such as those with nephrotic syndrome or patients receiving multiple doses of Amifostine for Injection (see ADVERSE REACTIONS). If necessary, calcium supplements can be administered.

PRECAUTIONS

General

Patients should be adequately hydrated prior to the Amifostine for Injection infusion and blood pressure should be monitored (see DOSAGE AND ADMINISTRATION).

The safety of Amifostine for Injection administration has not been established in elderly patients, or in patients with preexisting cardiovascular or cerebrovascular conditions such as ischemic heart disease, arrhythmias, congestive heart failure, or history of stroke or transient ischemic attacks. Amifostine should be used with particular care in these and other patients in whom the common amifostine adverse effects of nausea/vomiting and hypotension may be more likely to have serious consequences.

Prior to chemotherapy, Amifostine for Injection should be administered as a 15-minute infusion (see DOSAGE AND ADMINISTRATION). Blood pressure should be monitored every 5 minutes during the infusion, and thereafter as clinically indicated.

Prior to radiation therapy, Amifostine for Injection should be administered as a 3-minute infusion (see DOSAGE AND ADMINISTRATION). Blood pressure should be monitored at least before and immediately after the infusion, and thereafter as clinically indicated.

Cutaneous Reactions

Cutaneous reactions may require permanent discontinuation of Amifostine for Injection or urgent dermatologic consultation and biopsy (see below).

Cutaneous evaluation of the patient prior to each Amifostine for Injection administration should be performed with particular attention paid to the development of the following:

- Any rash involving the lips or involving mucosa not known to be due to another etiology (e.g., radiation mucositis, herpes simplex, etc.)
- Erythematous, edematous, or bullous lesions on the palms of the hands or soles of the feet and/or other cutaneous reactions on the trunk (front, back, abdomen)
- Cutaneous reactions with associated fever or other constitutional symptoms

Cutaneous reactions must be clearly differentiated from radiation-induced dermatitis and from cutaneous reactions related to an alternate etiology. Amifostine for Injection should be permanently discontinued for serious or severe cutaneous reactions (see WARNINGS and ADVERSE REACTIONS) or for cutaneous reactions associated with fever or other constitutional symptoms not known to be due to another etiology. Amifostine should be withheld and dermatologic consultation and biopsy considered for cutaneous reactions or mucosal lesions of unknown etiology appearing outside of the injection site or radiation port and for erythematous, edematous or bullous lesions on the palms of the hand or soles of the feet. Reinitiation of amifostine should be at the physician's discretion based on medical judgment and appropriate dermatologic evaluation.

Allergic Reactions

In case of severe acute allergic reactions Amifostine for Injection should be immediately and permanently discontinued. Epinephrine and other appropriate measures should be available for treatment of serious allergic events such as anaphylaxis.

Drug Interactions

Special consideration should be given to the administration of Amifostine for Injection in patients receiving antihypertensive medications or other drugs that could cause or potentiate hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long term animal studies have been performed to evaluate the carcinogenic potential of amifostine. Amifostine was negative in the Ames test and in the mouse micronucleus test. The free thiol metabolite was positive in the Ames test with S9 microsomal fraction in the TA1535 *Salmonella typhimurium* strain and at the TK locus in the mouse L5178Y cell assay. The metabolite was negative in the mouse micronucleus test and negative for clastogenicity in human lymphocytes.

Pregnancy

Pregnancy Category C. Amifostine has been shown to be embryotoxic in rabbits at doses of 50 mg/kg, approximately sixty percent of the recommended dose in humans on a body surface area basis. There are no adequate and well-controlled studies in pregnant women. Amifostine for Injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

No information is available on the excretion of amifostine or its metabolites into human milk. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants, it is recommended that breast feeding be discontinued if the mother is treated with Amifostine for Injection.

Pediatric Use

The safety and effectiveness in pediatric patients have not been established.

Geriatric Use

The clinical studies did not include sufficient number of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy in elderly patients.

ADVERSE REACTIONS

Controlled Trials

In the randomized study of patients with ovarian cancer given Amifostine for Injection at a dose of 910 mg/m² prior to chemotherapy, transient hypotension was observed in 62% of patients treated. The mean time of onset was 14 minutes into the 15-minute period of amifostine infusion, and the mean duration was 6 minutes. In some cases, the infusion had to be prematurely terminated due to a more pronounced drop in systolic blood pressure. In general, the blood pressure returned to normal within 5-15 minutes. Fewer than 3% of patients discontinued amifostine due to blood pressure reductions. In the randomized study of patients with head and neck cancer given amifostine at a dose of 200 mg/m² prior to radiotherapy, hypotension was observed in 15% of patients treated. (see TABLE 6)

TABLE 6
Incidence of Common Adverse Events in Patients Receiving Amifostine for Injection

	Phase III Ovarian Cancer Trial (WR-1) 910 mg/m²		Phase III Head and Neck Cancer Trial (WR-38) 200 mg/m²	
	Per Patient	Per Infusion	Per Patient	Per Infusion
Nausea/Vomiting				
≥Grade 3	36/122 (30%)	53/592 (9%)	12/150 (8%)	13/4314 (<1%)
All Grades	117/122 (96%)	520/592 (88%)	80/150 (53%)	233/4314 (5%)
Hypotension				
≥Grade 3[a]	10/122 (8%)		4/150 (3%)	
All Grades	75/122 (61%)	159/592 (27%)	22/150 (15%)	46/4314 (1%)

[a] According to protocol-defined criteria. WR-1: requiring interruption of infusion; WR-38: drop of >20mm Hg.

In the randomized study of patients with head and neck cancer, 17% (26/150) discontinued Amifostine for Injection due to adverse events. All but one of these patients continued to receive radiation treatment until completion.

Hypotension that requires interruption of the Amifostine for Injection infusion should be treated with fluid infusion and postural management of the patient (supine or Trendelenburg position). 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 can be administered. Short term, reversible loss of consciousness has been reported rarely.

Nausea and/or vomiting occur frequently after Amifostine for Injection infusion and may be severe. In the ovarian cancer randomized study, the incidence of severe nausea/vomiting on day 1 of cyclophosphamide-cisplatin chemotherapy was 10% in patients who did not receive amifostine, and 19% in patients who did receive amifostine. In the randomized study of patients with head and neck cancer, the incidence of severe nausea/vomiting was 8% in patients who received amifostine and 1% in patients who did not receive amifostine.

Decrease in serum calcium concentrations is a known pharmacological effect of Amifostine for Injection. At the recommended doses, clinically significant hypocalcemia was reported in 1% of patients in the randomized head and neck cancer study (see WARNINGS).

Other effects, which have been described during, or following Amifostine for Injection infusion are flushing/feeling of warmth, chills/feeling of coldness, malaise, fever, rash, dizziness, somnolence, hiccups and sneezing. These effects have not generally precluded the completion of therapy.

Clinical Trials and Pharmacovigilance Reports

Allergic reactions characterized by one or more of the following manifestations have been observed during or after Amifostine for Injection administration: hypotension, fever, chills/rigors, dyspnea, hypoxia, chest tightness, cutaneous eruptions, pruritus, urticaria and laryngeal edema. Cutaneous eruptions have been commonly reported during clinical trials and were generally non-serious. Serious, sometimes fatal skin reactions including erythema multiforme, and in rare cases, exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis have also occurred. The reported incidence of serious skin reactions associated with amifostine is higher in patients receiving amifostine as a radioprotectant than in patients receiving amifostine as a chemoprotectant. Rare anaphylactoid reactions and cardiac arrest have also been reported.

Hypotension, usually brief systolic and diastolic, has been associated with one or more of the following adverse events: apnea, dyspnea, hypoxia, tachycardia, bradycardia, extrasystoles, chest pain, myocardial ischemia and convulsion. Rare cases of renal failure, myocardial infarction, respiratory and cardiac arrest have been observed during or after hypotension. (See WARNINGS and PRECAUTIONS)

Rare cases of arrhythmias such as atrial fibrillation/flutter and supraventricular tachycardia have been reported. These are sometimes associated with hypotension or allergic reactions.

Transient hypertension and exacerbations of preexisting hypertension have been observed rarely after Amifostine for Injection administration.

Seizures and syncope have been reported rarely. (See WARNINGS and PRECAUTIONS)

OVERDOSAGE

In clinical trials, the maximum single dose of Amifostine for Injection was 1300 mg/m². No information is available on single doses higher than this in adults. In the setting of a clinical trial, pediatric patients have received single amifostine doses of up to 2700 mg/m². At the higher doses, anxiety and reversible urinary retention occurred.

Administration of Amifostine for Injection at 2 and 4 hours after the initial dose has not led to increased nausea and vomiting or hypotension. The most likely symptom of overdosage is hypotension, which should be managed by infusion of normal saline and other supportive measures, as clinically indicated.

DOSAGE AND ADMINISTRATION

For Reduction of Cumulative Renal Toxicity with Chemotherapy:

The recommended starting dose of Amifostine for Injection is 910 mg/m² administered once daily as a 15-minute i.v. infusion, starting 30 minutes prior to chemotherapy.

The 15-minute infusion is better tolerated than more extended infusions. Further reductions in infusion times for chemotherapy regimens have not been systematically investigated.

Patients should be adequately hydrated prior to Amifostine for Injection infusion and kept in a supine position during the infusion. Blood pressure should be monitored every 5 minutes during the infusion, and thereafter as clinically indicated.

The infusion of Amifostine for Injection should be interrupted if the systolic blood pressure decreases significantly from the baseline value as listed in the guideline below:

Guideline for Interrupting Amifostine for Injection Infusion Due to Decrease in Systolic Blood Pressure

	Baseline Systolic Blood Pressure (mm Hg)				
	<100	100-119	120-139	140-179	≥180
Decrease in systolic blood pressure during infusion of Amifostine for Injection (mm Hg)	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 for Injection may be administered. If the full dose of amifostine cannot be administered, the dose of amifostine for subsequent chemotherapy cycles should be 740 mg/m².

It is recommended that antiemetic medication, including dexamethasone 20 mg i.v. and a serotonin $5HT_3$ receptor antagonist, be administered prior to and in conjunction with Amifostine for Injection. Additional antiemetics may be required based on the chemotherapy drugs administered.

For Reduction of Moderate to Severe Xerostomia from Radiation of the Head and Neck:

The recommended dose of Amifostine for Injection is 200 mg/m² administered once daily as a 3-minute i.v. infusion, starting 15-30 minutes prior to standard fraction radiation therapy (1.8-2.0 Gy).

Patients should be adequately hydrated prior to Amifostine for Injection infusion. Blood pressure should be monitored at least before and immediately after the infusion, and thereafter as clinically indicated.

It is recommended that antiemetic medication be administered prior to and in conjunction with Amifostine for Injection. Oral $5HT_3$ receptor antagonists, alone or in combination with other antiemetics, have been used effectively in the radiotherapy setting.

Reconstitution

Amifostine for Injection is supplied as a sterile lyophilized powder requiring reconstitution for intravenous infusion. Each single-use vial contains 500 mg of amifostine on the anhydrous basis.

Prior to intravenous injection, Amifostine for Injection is reconstituted with 9.7 mL of sterile 0.9% Sodium Chloride Injection, USP. The reconstituted solution (500 mg amifostine/10 mL) is chemically stable for up to 5 hours at room temperature (approximately 25°C) or up to 24 hours under refrigeration (2°C to 8°C).

Amifostine for Injection prepared in polyvinylchloride (PVC) bags at concentrations ranging from 5 mg/mL to 40 mg/mL is chemically stable for up to 5 hours when stored at room temperature (approximately 25°C) or up to 24 hours when stored under refrigeration (2°C to 8°C).

CAUTION: Parenteral products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not use if cloudiness or precipitate is observed.

Incompatibilities

The compatibility of Amifostine for Injection with solutions other than 0.9% Sodium Chloride for Injection, or Sodium Chloride solutions with other additives, has not been examined. The use of other solutions is not recommended.

HOW SUPPLIED

Amifostine for Injection is supplied as a sterile lyophilized powder in 10 mL single-use vials (NDC 55390-308-03). Each single-use vial contains 500 mg of amifostine on the anhydrous basis. The vials are available packaged as follows:

3 pack - 3 vials per carton (NDC 55390-308-03)

Store the lyophilized dosage form at Controlled Room Temperature 20°-25°C (68°-77°F) [See USP].

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