National PBM Drug Guidance

PROMETHAZINE HCL INJECTION, USP (PHENERGAN®)

VHA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel

The following recommendations are based on current medical evidence and expert opinion from clinicians. The content of the document is dynamic and will be revised as new clinical data becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician should utilize this guidance and interpret it in the clinical context of the individual patient.

EXECUTIVE SUMMARY

Issue:
Serious tissue injury resulting in limb impairment with possible loss of the extremity has been associated with promethazine HCl injection.

Etiology:
Accidental intra-arterial injection or perivascular extravasation during administration of promethazine HCl injection can lead to vascular and tissue damage.

Mode of Action:
The following mechanisms have been implicated: norepinephrine-mediated vasoconstriction; thrombosis; precipitation of drug out of solution; endothelial inflammation; direct cytotoxicity; and venous constriction. Regardless of the mechanism, a common element is thrombosis.

Signs/Symptoms:
Adverse events associated with tissue injury include: pain, burning, erythema, swelling, arteriospasm, thrombophlebitis, venous thrombosis, phlebitis, paralysis, abscess, nerve damage, tissue necrosis, and gangrene.

Safety:
There are 4 case reports in the published literature regarding serious tissue injury associated with IV promethazine. The first published case of accidental intra-arterial administration of promethazine and its effects appeared in 1967. This, along with the other reports, describes symptoms of pain and ischemia after medication injection caused by arterial spasm, chemical arteritis, thrombosis, and direct tissue injury leading to gangrene and eventual amputation. Of the four published cases, only one patient did not develop gangrene. In this case, promethazine was not administered intra-arterially, however, extravasation occurred. The Institute of Safe Medication Practices (ISMP) reported 4 more recent cases that were caused by accidental intra-arterial administration and resulted in gangrene leading to amputation (in 3 cases) or skin graft (in one case).

Recommendations:
VA MedSAFE recommendations include:

1. Local facilities must review their current practices regarding administration of promethazine HCl injection.
2. Local facilities must create individual protocols for use of promethazine HCl injection.
3. Local Pharmacy and Therapeutics (P&T) Committees must determine instances where use of promethazine HCl injection is absolutely necessary.
4. Providers and clinicians must refer to the *Protocol for the Use of Antiemetics to Prevent Chemotherapy-Induced Nausea and Vomiting and Post-Operative Nausea and Vomiting* at http://vaww.pbm.va.gov/criteria/antiemeticdosing.pdf for alternative agents, such as parenteral prochlorperazine and parenteral ondansetron.
5. If parenteral promethazine must be used, providers and clinicians must follow recommendations per the package insert, ISMP, and VA MedSAFE.
6. Establish safeguards and alerts at each step of the medication use process (ordering, verifying, dispensing, and administration) to prevent of the potential risk of tissue injury, limb impairment, and possible loss of extremity associated with the use of the injectable form of promethazine HCl.
7. Educate providers and other health care staff on the proper administration technique of promethazine HCl injection to prevent tissue injury.
8. Educate providers and other health care staff as to which signs/symptoms to monitor for inadvertent intra-arterial injection or perivascular extravasation.
9. Educate patients to report symptoms of pain or burning during or after the administration of promethazine HCl injection.

A majority of the sites in the VA have opted to keep promethazine HCl injection on their VISN formularies. As of the end of fiscal year 2006, the VA spent close to $300,000 on promethazine HCl injection. As this utilization data is based on Prime Vendor purchasing data, route of administration (either intramuscular or intravenous) cannot be determined. VA MedSAFE will monitor the utilization of this agent and any adverse events associated with administration of the agent.

INTRODUCTION [1, 2, 3]

Promethazine HCl has long been used by oral, intramuscular, and intravenous routes as a sedative, hypnotic, antiemetic, antiallergic, and anti-motion sickness agent. This phenothiazine derivative contains phenol and has an alkalinic pH of approximately 4.0-5.5, making it damaging to veins and tissues if used parenterally. As such, the preferred route of administration for the injectable form of promethazine is intramuscularly, via a large muscle.

Product labeling warns against subcutaneous and intra-arterial injection of promethazine as it can cause serious vascular, nerve, and soft-tissue injury (see Figures 1 and 2). Case reports describe inadvertent intra-arterial injection or extravasation causing chemical irritation of the surrounding tissues as manifested by devastating limb impairment with possible loss of the extremity. Management of severe cases has required surgical interventions such as skin grafting and amputation.

Several theories attempt to explain the various pathologic consequences secondary to intra-arterial injection. One mechanism involves crystallization and precipitation, due to the high alkalinity of the agent, causing arterial blockage that could result in severe spasm and eventual tissue necrosis. Another mode of action deals with norepinephrine release potentiating vessel spasm, intimal damage, and thrombosis. A further process relies on intravascular erythrocyte hemolysis, crystal formation, and platelet aggregation to cause tissue damage. There is also a method where arterial damage and thrombosis initiates tissue damage. This is supported by animal studies showing that surgical sympathectomy and heparinization reduces the area of gangrene. However, regardless of the cause of tissue injury, biopsies confirm that thrombosis had developed in all cases where tissue damage had occurred.

Unintentional intra-arterial injection involves a continuum of symptoms ranging from acute to chronic impairment. Pain, flushing, numbness, and weakness have occurred after the initial injection. Skin mottling, cramping, phlebitis, parasthesias, and motor deficits have developed within 24 hours. This has progressed to muscle swelling, digital edema, ischemic contractures, and reduced hand function within 36 hours. At two weeks, patients have demonstrated necrosis and gangrene requiring skin graft or amputation. Per the package insert, there is no proven successful management of accidental intra-arterial injection or perivascular extravasation.

Figure 1.

Figure 2 a.

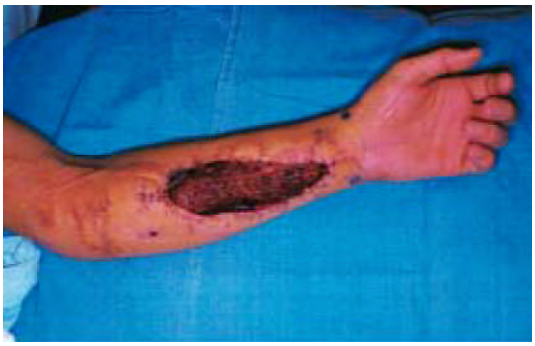
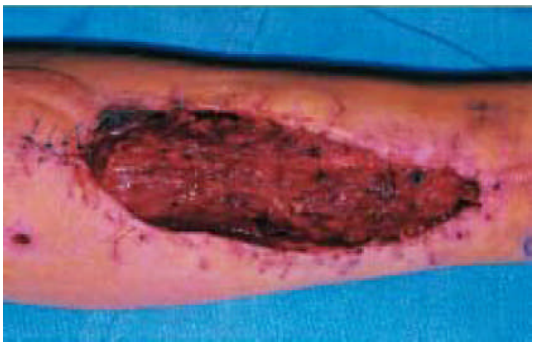


Figure 2 b.



PHARMACOLOGY/PHARMACOKINETICS [1]

Promethazine HCl is a phenothiazine agent with antihistaminic, sedative, antiemetic, anticholinergic and antimotion-sickness properties. Promethazine blocks dopaminergic (D2) receptors in the chemoreceptor trigger zone near the fourth ventricle. Promethazine also competitively blocks the H1 histamine receptor without affecting the release of histamine.

Parameter	
Onset	5 minutes (IV) 20 minutes (IM)
Duration of action	4-6 hours (affects may persist up to 12 hours)
Protein Binding	93%
Volume of distribution	171 L
Metabolism	Hepatic, (with sulfoxides of promethazine and N-desmethylpromethazine predominantly excreted in the urine)
Elimination Half-Life	9-16 hours after IV injection in healthy volunteers 9.8 ± 3.4 hours after IM injection in healthy volunteers

FDA APPROVED INDICATIONS [1]

- For use in amelioration of allergic conditions
  - Allergic reactions to blood or plasma
  - Anaphylaxis – as an adjunct to epinephrine and other standard measures after control of immediate symptoms
  - Uncomplicated allergic conditions where oral therapy is not possible or contraindicated
  - Improving physical function
- For use in the active treatment of motion sickness
- For use in preoperative, postoperative, and obstetric (during labor) settings
  - To prevent and control nausea and vomiting caused by specific anesthesia and surgical procedures
  - To control postoperative pain as an adjunct to analgesics
  - Sedation
  - Intravenously in special surgical situations (repeated bronchoscopy, ophthalmic surgery, and poor-risk patients) with reduced amounts of meperidine or other narcotic analgesic as an adjunct to anesthesia and analgesia

CURRENT VA NATIONAL FORMULARY ALTERNATIVES [4]

	Formulary	Non-Formulary	Restrictions
Antihistaminic-Anticholinergic Agents			
Dimenhydrinate (Dramamine ®)		X	
Diphenhydramine (Benadryl ®)	INJ, TAB, CAP		
Hydroxyzine (Vistaril ®)	INJ, TAB, CAP		
Trimethobenzamide (Tigan ®)	CAP		X – Restricted to use with apomorphine

Phenothiazines	INJ, TAB, SOLN		
Chlorpromazine (Thorazine ®)	INJ, TAB, SUPP		
Prochlorperazine (Compazine ®)			
Promazine (Sparine ®)		X	
Thiethylperazine (Torecan ®)		X	
Promethazine (Phenergan®)	INJ, TAB, SUPP, SYRUP		
Butyrophenones			
Droperidol (Inapsine ®)	INJ		
Haloperidol (Haldol ®)	INJ, TAB, LIQUID		
Corticosteroids			
Dexamethasone (Decadron ®)	INJ, TAB, LIQUID		
Benzodiazepines			
Lorazepam (Ativan ®)	INJ, TAB		
Selective Serotonin Antagonists			
Ondansetron (Zofran ®)	INJ, TAB		X
Granisetron (Kytril ®)		X	
Dolasetron (Anzemet ®)			
Miscellaneous Agents			
Metoclopramide (Reglan ®)	INJ, TAB, LIQUID		

DOSAGE AND ADMINISTRATION [1]

- **DOSAGE**
  - **Allergic Conditions**
    - 25mg injection x 1. Dose may be repeated within 2 hours if necessary. Additional continued therapy should occur via the oral route.
  - **Sedation**
    - 25mg-50mg injection for nighttime sedation in hospitalized adult patients.
  - **Nausea and Vomiting**
    - 12.5mg – 25mg injection no more than every 4 hours. Can be given either IM or IV. Dosage of analgesics or barbiturates to be reduced accordingly.
  - **Preoperative and Postoperative Use**
    - 25mg – 50mg injection as an adjunct to preoperative or postoperative medication. Dosage of analgesics or barbiturates to be reduced accordingly.
  - **Obstetrics**
    - **Early labor:** 50mg injection for sedation and relief of apprehension.
    - **During labor:** 25mg – 75mg (average dose 50mg) injection IM or IV with an appropriately reduced dose of desired narcotic. May be repeated once or twice at 4-hour intervals in the course of a normal labor. Maximum total dose during a 24-hour period for patients during labor = 100mg injection.
  - **Pediatrics**
    - **≥2 years of age:** Dose should not exceed half that of the suggested adult dose. As an adjunct to premedication, the suggested dose is 0.5mg per lb of body weight in

combination with an appropriately reduced dose of narcotic or barbiturate and the appropriate dose of an atropine-like drug.

- **IMPORTANT NOTES ON ADMINISTRATION**
  - **Routes:**
    - **Preferred parenteral route of administration = Deep intramuscular injection (IM).**
    - **Not for subcutaneous (SQ) administration (contraindicated). May result in tissue necrosis.**
    - **Proper intravenous (IV) use:**
      - **Concentration not to exceed 25mg/mL**
      - **Rate not to exceed 25mg/minute**
      - **Preferable to inject through the tubing of an intravenous infusion set that is known to be functioning satisfactorily**
    - **Unintentional intra-arterial injection can result in gangrene of the affected extremity.**
    - **Injections into or near a nerve may result in permanent tissue damage.**
  - **Storage and stability:**
    - **Do not use Promethazine HCl Injection if solution has developed color or contains precipitate.**
    - **Product is light sensitive.**

ADVERSE EVENTS (SAFETY DATA) [1-2, 5-8]

- **TOLERABILITY ISSUES**

There are 4 case reports in the published literature regarding serious tissue injury associated with IV promethazine. The first published case of accidental intra-arterial administration of promethazine and its effects appeared in 1967. This, along with the other reports, describes symptoms of pain and ischemia after medication injection caused by arterial spasm, chemical arteritis, thrombosis, and direct tissue injury leading to gangrene and eventual amputation. Of the four published cases, only one patient did not develop gangrene. In this case, promethazine was not administered intra-arterially, however, extravasation occurred. The Institute of Safe Medication Practices (ISMP) reported 4 more recent cases that were caused by accidental arterial administration and resulted in gangrene leading to amputation (in 3 cases) or skin graft (in one case).

For further details, refer to *APPENDIX: CASE REPORTS*.

- **INFUSION RELATED REACTIONS AND HYPERSENSITIVITY REACTIONS**

  - Promethazine HCl Injection can cause severe chemical irritation and damage to tissues, regardless of the route of administration due to perivascular extravasation, unintentional intra-arterial injection, and intraneuronal or perineuronal infiltration.
  - Signs and symptoms include:
    - Burning
    - Pain
    - Erythema
    - Abscesses
    - Tissue Necrosis
    - Gangrene

- Nerve damage ranging from temporary sensory loss to palsies, paralysis, or permanent tissue damage has resulted requiring surgical intervention such as fasciotomy, skin graft, and/or amputation.
- Inadvertent Intra-Arterial Injection
  - Pain, severe chemical irritation, severe spasm of distal vessels, and resultant gangrene requiring amputation has been reported.
  - Intended route of administration was intravenous, but perivascular extravasation or arterial placement of the needle occurred.
  - No proven successful management exists for unintentional intra-arterial injection or perivascular extravasation.

PRECAUTIONS/CONTRAINDICATIONS [1]

- **PRECAUTIONS**
  - Administration to pediatric patients ≥ 2 years of age. Concomitant administration of other drugs with respiratory depressant effects should be avoided.
  - Contains sodium metabisulfite. Possible sulfite sensitivity, including anaphylactic symptoms and life-threatening or less severe asthma episodes.
  - CNS depression. May impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a vehicle or operating machinery.
  - Respiratory depression in patients with compromised respiratory function (i.e., COPD, sleep apnea).
  - May lower seizure threshold.
  - Possible bone-marrow depression. Leukopenia and agranulocytosis have been reported, usually in association with other known marrow-toxic agents.
  - Neuroleptic Malignant Syndrome (NMS) has been reported when promethazine HCl has been used alone or in combination with antipsychotic drugs.
  - Use in pediatric patients ≥2 years due to possible respiratory depression and apnea. Concomitant administration of promethazine with other respiratory depressants has an association with respiratory depression, and sometimes death, in pediatric patients.
  - The use of promethazine HCl injection should be avoided in pediatric patients whose signs and symptoms may suggest Reye's syndrome or other hepatic diseases.
  - Injection site reactions, causing severe chemical irritation and damage to tissues regardless of route of administration. Can also be caused by perivascular extravasation, unintentional intra-arterial injection, and intraneuronal or perineuronal infiltration.
  - Inadvertent intra-arterial injection has resulted in pain, severe chemical irritation, severe spasm of distal vessels, and resultant gangrene requiring amputation.
  - Product is light sensitive and should be visually inspected before use.
  - Should be avoided in patients with sleep apnea.
  - Administration of promethazine has been associated with reported cholestatic jaundice.
  - Should be used cautiously in patients with cardiovascular disease or impairment of liver function.
  - Caution in patients with narrow-angle glaucoma, prostatic hypertrophy, stenosing peptic ulcer, pyloroduodenal obstruction, and bladder-neck obstruction.
  - Dosage should be reduced in geriatric patients approximately 60 years of age or older.
  - Pregnancy category C.

- **CONTRAINDICATIONS**
  - Pediatric patients less than 2 years of age due to the potential for fatal respiratory depression;
  - Comatose states
  - Patients who have demonstrated an idiosyncratic reaction or hypersensitivity to promethazine or other phenothiazines
  - Intra-arterial injection – may result in arteriospasm and possible gangrene
  - Subcutaneous route – may result in chemical irritation and necrotic lesions

DRUG INTERACTIONS [1]

- **Drug – Drug Interactions**
  - CNS Depressants – Promethazine HCl Injection may increase, prolong, or intensify the sedative action of CNS depressants, such as alcohol, sedative/hypnotics (including barbiturates), general anesthetics, narcotics, narcotic analgesics, tricyclic antidepressants, and tranquilizers. When used concomitantly with Promethazine HCl, the dose of barbiturates should be reduced by one-half, and the dose of narcotics should be reduces by one-quarter to one-half.
  - Epinephrine – Should not be used to treat hypotension associated with Promethazine HCl Injection overdose due to the potential for promethazine HCl to reverse epinephrine's vasopressor effect.
  - Anticholinergics – Concomitant use should be undertaken with caution.
  - Monoamine Oxidase Inhibitors (MAOI) – increased incidence of extrapyramidal effects have been reported with concomitant use.
- **Drug – Lab Interactions**
  - Pregnancy tests using immunological reactions between HCG and anti-HCG may result in false-negative or false-positive interpretations
  - Glucose Tolerance Test – An increase in blood glucose has been reported in patients receiving promethazine HCl.

PHARMACOECONOMIC ANALYSIS

No data exists in the published literature regarding the pharmacoeconomics of promethazine.

ACQUISITION COSTS [4]

**** Costs as reported below reflect current pricing only. Please refer to the PBM website (vaww.pbm.med.va.gov or www.vapbm.org) for updated cost information.***

Parenteral Product	Cost/Milliliter	Adult Dose	Route of Administration	Schedule
Antihistaminic-Anticholinergic Agents				
Dimenhydrinate (Dramamine ®) 50mg/mL	$1.53	50-100 mg	IM	Q 4-6 H PRN for motion sickness
Diphenhydramine (Benadryl ®) 50mg/mL	$0.62-$1.90	10-50 mg	IM/IV	Q 2-3 H, MAX 400mg/day
Hydroxyzine (Vistaril ®) 25mg/mL 50mg/mL	$0.38 $0.05-0.42	25-100 mg	IM	Q 6 H PRN
Trimethobenzamide (Tigan ®) 100mg/mL	$1.56-$16.44	200 mg	IM	TID-QID PRN

Phenothiazines				
Chlorpromazine (Thorazine ®)		25-50 mg (px)	IM	Q 3-4 H PRN before surgery;
25mg/mL	$0.87-$1.57	12.5 mg (tx)	IM	X 1 during surgery; repeat in 30 minutes prn, and if no hypotension occurs ;
		2mg (tx)	IV	Per fractional injection at 2 minute intervals, do not exceed 25 mg
Prochlorperazine (Compazine ®)		5-10 mg	IM	3-4 times daily prn;
5mg/mL edisylate	$0.74-$0.86			1-2 hours before induction of anesthesia (repeat once in 30 minutes prn);
5mg/mL	$0.85-$0.95			
		2.5 – 10 mg	IVF	Not to exceed 10mg in a single dose or 40mg/day;
			IV	15-30 minutes before induction of anesthesia (repeat once in 30 minutes prn) or to control acute symptoms during or after surgery (repeat once prn)
Promazine (Sparine ®)	Not in NDF	25-50 mg	IM	Q 6-8 H PRN
Thiethylperazine (Torecan ®)	Not in NDF	10mg	IM	QD-TID, or shortly before the termination of anesthesia
Promethazine (Phenergan ®)				
25mg/mL	$0.59-$1.21	12.5-25 mg	IM/IV	Q 4-6 H PRN
50mg/mL	$0.72-$1.21			
Butyrophenones				
Droperidol (Inapsine ®)		2.5 mg	IM/IV	May repeat 1.25mg dose based on patient response
2.5mg/mL	$0.33-$0.61			
Haloperidol (Haldol ®)		4 mg	IM	Q 6 H for chemotherapy induced N/V
50mg/mL	$2.14-$29.01			
100mg/mL	$3.20-$53.15			
5mg/mL	$$1.29-$6.81			
Corticosteroids				
Dexamethasone (Decadron ®)		20 mg	IV	X 1 prior to chemotherapy;
4mg/mL	$0.11-$0.80	8 mg	IV	BID x 3 days after chemotherapy
10mg/mL	$0.12-$1.80			
Benzodiazepines				
Lorazepam (Ativan ®)		0.25-0.5	IM/IV	30-35 minutes prior to chemotherapy
2mg/mL	$0.01-$0.97	mg/kg		
4mg/mL	$0.94-$1.73	(4 mg max)		
Selective Serotonin Antagonists				

Ondansetron (Zofran ®) 2mg/mL		4 mg	IM/IV	Prior to the induction of anesthesia or postoperatively;
	$6.21-$6.49	32 mg	IV	30 minutes prior to chemo;
		0.15mg/kg	IV	30 minutes prior to chemo repeated 4 and 8 hours after the first dose
Granisetron (Kytril ®) 1mg/mL	$36.48-$50.77	1 mg	IV	Before induction of anesthesia or immediately before reversal of anesthesia;
		10mcg/kg	IV	30 minutes prior to chemo
Dolasetron (Anzemet ®) 12.5/0.625mL	$7.17-$8.18	12.5 mg	IV	Intraoperatively 15 minutes prior to cessation of anesthesia;
20mg/mL	$1.09-$1.17			
		1/8mg.kg or 100mg	IV	30 minutes prior to chemo
Miscellaneous Agents				
Metoclopramide (Reglan ®) 5mg/mL	$0.10-$0.20	10-20mg/kg 1-2 mg/kg/dose	IM/IV	Q 4-6 H; Over 15 minutes administered 30 minutes prior to chemo and then Q 2 H x 2 doses, then Q 3 H X 3 doses

CONCLUSIONS [1-2, 9-14]

Promethazine can be administered intravenously with special precautions to avoid inadvertent arterial injection or extravasation. The manufacturer recommends that promethazine HCl injection should be administered in a concentration no more than 25mg/mL and at a rate no faster than 25mg/minute, using an intravenous infusion set with fully functioning tubing. The package insert states that the preferred parenteral route of administration is via intramuscular injection, but that special surgical situations may necessitate intravenous use, such as: repeated bronchoscopy, ophthalmic surgery, and poor-risk patients, with reduced amounts of meperidine or other narcotic analgesics as an adjunct to anesthesia and analgesia.

The Institute for Safe Medication Practices (ISMP) has also released recommendations to minimize or prevent serious tissue injury with intravenous promethazine:

1. Limit the concentration to ≤ 25mg/mL.
2. Limit the dose with starting doses as low as 6.25mg – 12.5mg, especially for elderly patients.
3. Dilute the drug to reduce potential vesicant effects.
4. Avoid hand or wrist vessels and use large patent veins via a central venous access site.
5. Inject into the port furthest from the patient's vein.
6. Administer slowly over 10-15 minutes.
7. Revise order forms to include actions needed to minimize tissue injury.
8. Educate patients to notify healthcare staff of pain or burning during or after the injection.
9. Create computer generated alerts during the ordering process regarding the safety hazards and necessary precautions to minimize tissue injury.
10. Although no successful management exists, treat accidental intra-arterial injection or extravasation by sympathetic block and heparinization.

11. Use alternative agents to treat post-operative nausea and vomiting.
12. Remove promethazine HCl injection from the formulary.

A randomized, double-blind clinical trial compared intravenous prochlorperazine with intravenous promethazine for uncomplicated nausea and vomiting in the emergency department. Results showed that intravenous prochlorperazine was found to be more effective with better control of nausea and vomiting, fewer treatment failures, and lesser sedative action compared to promethazine. No tissue injury and associated limb complications associated with administration of intravenous promethazine or intravenous prochlorperazine occurred within this cohort (N=84). According to the literature, accidental intra-arterial administration of chlorpromazine, promazine, and hydroxyzine have also resulted in gangrene.

RECOMMENDATIONS

VA MedSAFE recommendations include:

1. Local facilities must review their current practices regarding administration of promethazine HCl injection.
2. Local facilities must create individual protocols for use of promethazine HCl injection.
3. Local Pharmacy and Therapeutics (P&T) Committees must determine instances where use of promethazine HCl injection is absolutely necessary.
4. Providers and clinicians must refer to the *Protocol for the Use of Antiemetics to Prevent Chemotherapy-Induced Nausea and Vomiting and Post-Operative Nausea and Vomiting* at http://vaww.pbm.va.gov/criteria/antiemeticdosing.pdf for alternative agents, such as parenteral prochlorperazine and parenteral ondansetron.
5. If promethazine must be used, providers and clinicians must follow recommendations per the package insert, ISMP, and VA MedSAFE.
6. Establish safeguards and alerts at each step of the medication use process (ordering, verifying, dispensing, and administration) to prevent of the potential risk of tissue injury, limb impairment, and possible loss of extremity associated with the use of the injectable form of promethazine HCl.
7. Educate providers and other health care staff on the proper administration technique of promethazine HCl injection to prevent tissue injury.
8. Educate providers and other health care staff as to which signs/symptoms to monitor for inadvertent intra-arterial injection or perivascular extravasation.
9. Educate patients to report symptoms of pain or burning during or after the administration of promethazine HCl injection.

A majority of the sites in the VA have opted to keep promethazine HCl injection on their VISN formularies. As of the end of fiscal year 2006, the VA spent close to $300,000 on promethazine HCl injection. As this utilization data is based on Prime Vendor purchasing data, route of administration (either intramuscular or intravenous) cannot be determined. VA MedSAFE will monitor the utilization of this agent and any adverse events associated with administration of the agent.

REFERENCES

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APPENDIX: CASE REPORTS

Patient Characteristics	Drug	Dose	Route of Administration	Concomitant medications	Type of Procedure	Outcome
Middle-aged woman	Promethazine	25mg	IV – via a left antecubital vessel	Meperidine HCl, 50mg	Not reported	Immediate pain in the distal forearm and hand, followed by discoloration, coldness, and numbness. Progressive gangrene of the fingers and thumb occurred with amputation through the distal forearm required seven weeks later.
64 y/o male	Promethazine	25mg	IV – via a 19-gauge regular needle in the right antecubital vein	N/A	Exploratory laparotomy; promethazine was given for a generalized skin reaction after abdominal incision.	Within 3 minutes, pt developed cyanosis of the forearm and fingers. Prolonged hospitalization with close monitoring for 4 days. Pt developed erythema, mild edema, and scattered patches of pallor on hand and forearm. Necrotic and gangrenous changes developed on the back of the hand and finger tips necessitating skin graft and eventual amputation of the 3rd, 4th, and 5th fingers at the distal interphalangeal joints.
43 y/o, 160 lb. female	Promethazine	25 mg	IV – via a catheter in the patient's right hand	N/A	Vaginal hysterectomy	12/17/96 – Pt c/o burning, swelling, and pain in right hand after receiving the dose; nurse observed redness, swelling, and bluish discoloration around the IV site. Pt was treated with elevation of the right hand, ganglion blockade, and corticosteroid therapy. Pt was monitored for 5 days, where pain and edema went down while range of motion improved. No accidental intra-arterial injection was diagnosed. Extravasation of promethazine only. Pt was discharged in the sixth day. No surgical intervention was needed. 06/1997 – pt still c/o continued numbness in the 3rd and 4th digits of

						her right hand. Pt dx'd with carpal tunnel of both wrists and shoulder sx secondary to hand injury. 11/1998 – pt c/o mild cold intolerance.
25 y/o, 265 lb. female	Promethazine	25 mg	IV – via a line in the left dorsum of the patient's hand	N/A	OB/GYN – dilation and evacuation under intravenous sedation.	06/02/03 - Pt c/o severe burning in left wrist and hand, followed by blotchy cyanosis and discoloration, which persisted for 12 hours after which pt was transferred to a tertiary care hospital for treatment for accidental intra-arterial injection (including morphine, temporary sympathectomy via ganglion and nerve blocks, anticoagulation therapy, nitropaste, and limb elevation. Pt was release and received abx x 2 weeks. 06/15/03 - Pt persisted with fevers, chills, and the distal tips of her left index finger, ring finger, and small finger and thumb were fully demarcated. 06/23/03 - Amputation of gangrenous tissue with skin grafts.
19 y/o female	Phenergan	Not Reported	IV	N/A	Administered in the ER for relief of flu-like symptoms	Immediate pain and discoloration leading to prolonged hospitalization for 30 days with eventual amputation of her thumb, index finger, and top of her middle finger.
Not Reported	Promethazine	12.5 mg	IV site in the hand	N/A	Not Reported	Burning sensation leading to necrosis eventually requiring skin grafts and physical rehabilitation.
Not Reported	Phenergan	Not Reported	Not reported	Not Reported	Not Reported	Amputation of 2 fingers.
Female	Phenergan	Not Reported	IV	Not Reported	Administered in the ER for treatment of a migraine	Circulatory problems with progressive gangrene leading to amputation of her arm.