HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use MEPERGAN INJECTION safely and effectively. See full prescribing information for MEPERGAN INJECTION.

MEPERGAN (meperidine HCl and promethazine HCl) injection, for intramuscular or intravenous use, CII

Initial U.S. Approval: 1961

WARNING: SERIOUS AND LIFE-THREATENING RISKS FROM USE OF MEPERGAN

See full prescribing information for complete boxed warning.

- **MEPERGAN Injection exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patient's risk before prescribing and reassess regularly for these behaviors and conditions (5.1)**
- **Serious, life-threatening, or fatal respiratory depression may occur with use of MEPERGAN Injection, especially initiation or following a dosage increase. To reduce the risk of respiratory depression, proper dosing and titration of MEPERGAN Injection are essential. (5.2)**
- **Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate. (5.3)**
- **Advise pregnant woman using opioids for an extended period of time of the risk of Neonatal Opioid Withdrawal Syndrome, which may be life-threatening if not recognized and treated. Ensure that management by neonatology experts will be available at delivery (5.4).**
- **Concomitant use with CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) can result in fatal overdose of MEPERGAN Injection (5.5)**
- **Concomitant use of MEPERGAN Injection with Monoamine oxidase (MAO) inhibitors can result in coma, severe respiratory depression, cyanosis and hypotension. Use of MEPERGAN Injection with MAO inhibitors is contraindicated. (5.6, 7)**

----------RECENT MAJOR CHANGES----------

Boxed Warning	12/2025
Indications and Usage (1)	12/2025
Dosage and Administration (2.4)	12/2025
Warnings and Precautions (5.1, 5.2, 5.3, 5.13, 5.14, 5.15)	12/2025

----------INDICATIONS AND USAGE----------

MEPERGAN Injection contains meperidine, an opioid agonist, and promethazine, a phenothiazine. MEPERGAN Injection is indicated for:

- the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.
- as a preanesthetic medication when analgesia and sedation are indicated.
- as an adjunct to local and general anesthesia.

Limitations of Use

Because of the risks of addiction, abuse, misuse, overdose, and death, which can occur at any dosage or duration and persist over the course of therapy, reserve opioid analgesics, including MEPERGAN Injection for use in patients for whom alternative treatment options are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. (1, 5.1)

----------DOSAGE AND ADMINISTRATION----------

- MEPERGAN Injection should be prescribed only by healthcare professionals who are knowledgeable about the use of opioids and how to mitigate the associated risks. (2.1)
- Use the lowest effective dosage for the shortest duration of time consistent with individual patient treatment goals. Reserve titration to higher doses of MEPERGAN Injection for patients in whom lower doses are insufficiently effective and in whom the expected benefits of using a higher does opioid clearly outweigh the substantial risks. (2.1, 5)
- Many acute pain conditions (e.g., the pain that occurs with a number of surgical procedures or acute musculoskeletal injuries) require no more than a few days of an opioid analgesic. Clinical guidelines on opioid prescribing for some acute pain conditions are available. (2.1)
- Initiate the dosing regimen for each patient individually, taking into account the patient's underlying cause and severity of pain, prior analgesic treatment and response, and risk factors for addiction, abuse and misuse. (2.1, 5.1)
- Respiratory depression can occur at any time during opioid therapy, especially when initiating and following dosage increases with MEPERGAN Injection. Consider this risk when selecting an initial dose and when making dose adjustments. (2.2, 5.2).
- Initiate treatment as follows:
  Adult: 1 to 2 mL (25 to 50 mg of each component) per single injection which can be repeated every 3 to 4 hours (2.2)
  Children 12 Years of Age and Under: 0.5 mg of each component per pound of body weight. The dosage may be repeated every 3 to 4 hours as necessary (2.2)
- Titrate the dose based upon the individual patient's response to their initial dose of MEPERGAN Injection. (2.2, 5)
- Periodically reassess patients receiving MEPERGAN Injection to evaluate the continued need for opioid analgesics to maintain pain control, for the signs and symptoms of adverse reactions, and for the development of addiction, abuse or misuse (2.3)
- Do not rapidly reduce or abruptly discontinue MEPERGAN Injection in a physically dependent patient (2.4, 5.15)

----------DOSAGE FORMS AND STRENGTHS----------

- Injectable, Tubex blunt point cartridge, 2 mL. Each mL contains 25 mg meperidine hydrochloride and 25 mg promethazine hydrochloride.
- Injectable, multi-dose vial, 250 mg of meperidine HCl and 250 mg of promethazine HCl/10 mL (25 mg meperidine HCL and 25 mg promethazine HCl/mL) (3)

----------CONTRAINDICATIONS----------

- Significant respiratory depression (4)
- Acute or severe bronchial asthma in an unmonitored setting in absence of resuscitative equipment (4)
- Concurrent use of monoamine oxidase inhibitors (MAOI) or use of MAOIs within the last 14 days. (4)
- Known or suspected gastrointestinal obstruction, including paralytic ileus (4)
- Hypersensitivity to meperidine or promethazine (4)
- Administration by intra-arterial injection, due to the likelihood of severe arteriospasm and the possibility of resultant gangrene (4)
- Administration by the subcutaneous route; necrotic lesions have resulted (4)

----------WARNINGS AND PRECAUTIONS----------

- Opioid-Induced Hyperalgesia and Allodynia: Opioid-Induced Hyperalgesia (OIH) occurs when an opioid analgesic paradoxically causes an increase in pain, or an increase in sensitivity to pain. If OIH is suspected, carefully consider appropriately decreasing the dose of the current opioid analgesic or opioid rotation. (5.7)
- Serotonin Syndrome with Concomitant Use of Serotonergic Drugs: Potentially life-threatening condition could result from concomitant serotonergic drug administration. Discontinue MEPERGAN Injection if serotonin syndrome is suspected. (5.8)
- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Monitor closely, particularly during initiation and titration. (5.9)
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.10)
- Severe Hypotension: Monitor during dosage initiation and titration. Avoid use of MEPERGAN Injection in patients with circulatory shock. (5.11)
- Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness: Monitor for sedation and respiratory depression. Avoid use of MEPERGAN Injection in patients with impaired consciousness or coma. (5.12)

----------ADVERSE REACTIONS----------

Most serious adverse reactions were light-headedness, dizziness, sedation, nausea, vomiting, and sweating (6)

To report SUSPECTED ADVERSE REACTIONS, contact West-Ward Pharmaceuticals Corp. at 1-877-845-0689 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics: Avoid use with MEPERGAN Injection because they may reduce the analgesic effect of MEPERGAN Injection or precipitate withdrawal symptoms. (7)

See 17 for PATIENT COUNSELING INFORMATION

----------USE IN SPECIFIC POPULATIONS----------

Revised: 12/2025

- Pregnancy: May cause fetal harm. (8.1)
- Geriatric patients: Use caution during dose selection, starting at the low end of the dosing range while carefully monitoring for side effects. (8.5)

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS AND LIFE-THREATENING RISKS FROM USE OF MEPERGAN

Addiction, Abuse, and Misuse

Because the use of MEPERGAN Injection exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death, assess each patient's risk prior to prescribing and reassess all patients regularly for the development of these behaviors and conditions *[see Warnings and Precautions (5.1)]*.

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of MEPERGAN Injection, especially during the initiation or following a dosage increase. To reduce the risk of respiratory depression, proper dosing and titration of MEPERGAN are essential. *[see Warnings and Precautions (5.2)]*.

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of MEPERGAN Injection and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate *[*see *Warnings and Precautions (5.3), Drug Interactions (7)]*.

Neonatal Opioid Withdrawal Syndrome (NOWS)

Advise pregnant women using opioids for an extended period of time of the risk of Neonatal Opioid Withdrawal Syndrome, which may be life-threatening if not recognized and treated. Ensure that management by neonatology experts will be available at delivery *[see Warnings and Precautions (5.4)]*.

Cytochrome P450 3A4 Interaction

The concomitant use of MEPERGAN Injection with all cytochrome P450 3A4 inhibitors may result in an increase in meperidine plasma concentrations, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in meperidine plasma concentration. Regularly evaluate patients receiving MEPERGAN Injection and any CYP3A4 inhibitor or inducer [*see Warnings and Precautions (5.5), Drug Interactions (7)]*.

Concomitant Use of MEPERGAN Injection with Monoamine Oxidase (MAO) Inhibitors

Concomitant use of MEPERGAN Injection with monoamine oxidase (MAO) inhibitors can result in coma, severe respiratory depression, cyanosis, and hypotension. Use of MEPERGAN Injection with MAO inhibitors within last 14 days is contraindicated *[*see *Contraindications (4), Warnings and Precautions (5.6), Drug Interactions (7)]*.

1 INDICATIONS AND USAGE

MEPERGAN Injection is indicated as a preanesthetic medication when analgesia and sedation are indicated and as an adjunct to local and general anesthesia.

MEPERGAN Injection is indicated for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

Limitations of Use

Because of the risks of addiction, abuse, misuse, overdose, and death which can occur at any dosage or duration and persist over the course of therapy *[see Warning and Precautions (5.1)]*, reserve opioid analgesics, including

MEPERGAN Injection, for use in patients for whom alternative treatment options are ineffective, not tolerated or would be otherwise inadequate to provide sufficient management of pain.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

- MEPERGAN Injection should be prescribed only by healthcare professionals who are knowledgeable about the use of opioids and how to mitigate the associated risks.
- Use the lowest effective dosage for the shortest duration of time consistent with individual patient treatment goals [see *Warnings and Precautions* (5)]. Because the risk of overdose increases as opioid doses increase, reserve titration to higher doses of MEPERGAN Injection for patients in whom lower doses are insufficiently effective and in whom the expected benefits of using a higher dose opioid clearly outweigh the substantial risks.
- Many acute pain conditions (e.g., the pain that occurs with a number of surgical procedures or acute musculoskeletal injuries) require no more than a few days of an opioid analgesic. Clinical guidelines on opioid prescribing for some acute pain conditions are available.
- There is variability in the opioid analgesic dose and duration needed to adequately manage pain due both to the cause of the pain and to individual patient factors. Initiate the dosing regimen for each patient individually, taking into account the patient's underlying cause and severity of pain, prior analgesic treatment and response, and risk factors for addiction, abuse and misuse [*see Warning and Precautions (5.1)*].
- Respiratory depression can occur at any time during opioid therapy, especially when initiating and following dosage increases with MEPERGAN Injection. Consider this risk when selecting an initial dose and when making dose adjustments [*see Warning and Precautions (5.2)*].
- Inspect MEPERGAN Injection for particulate matter and discoloration prior to administration. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
- Barbiturates are not chemically compatible in solution with MEPERGAN (meperidine hydrochloride and promethazine hydrochloride) Injection and should not be mixed in the same syringe.
- MEPERGAN Injection is usually administered intramuscularly. However, in certain specific situations, the intravenous route may be employed.
- Inadvertent intra-arterial injection can result in gangrene of the affected extremity *[see Warnings and Precautions (5.20)]*. Subcutaneous administration is contraindicated, as it may result in tissue necrosis *[see Contraindications (4)]*. Injection into or near peripheral nerves may result in permanent neurological deficit.
- When used intravenously, the rate should not be greater than 1 mL of MEPERGAN (25 mg of each component) per minute; it is preferable to inject through the tubing of an intravenous infusion set that is known to be functioning satisfactorily.

TUBEX® BLUNT POINTE Sterile Cartridge Unit

The TUBEX® BLUNT POINTE™ Sterile Cartridge Unit is suitable for substances to be administered intravenously only. It is intended for use with Injection sets specifically manufactured as "needle-less" Injection systems. TUBEX® BLUNT POINTE™ is compatible with Abbott's LifeShield® pre-pierced reseal Injection site, Baxter's Interlink® Injection Site, and B. Braun Medical's SafSite® Reflux Valve. Consult manufacturer's recommendations regarding "Directions for Use" of the "needle-less" system. It is also intended for admixture with, and convenient administration of, various medicaments when using Drug Vial Adapters for "needle-less" Injection systems.

The TUBEX® Sterile Cartridge-Needle Unit is suitable for substances to be administered intravenously or intramuscularly.

The TUBEX" Sterile Cartridge-Needle Unit is designed for single-dose use. VIALS should be used when required doses are fractions of a milliliter, as indicated below.

2.2 Initial Dosage

Initiating Treatment with MEPERGAN Injection

For Management of Pain

Intramuscular administration is preferred when repeated doses are required. If intravenous administration is required, dosage should be decreased and the injection made very slowly, preferably utilizing a diluted solution. The dose of MEPERGAN Injection should be proportionately reduced (usually by 25 to 50 percent) when administered concomitantly with phenothiazines and many other tranquilizers since they potentiate the action of MEPERGAN Injection.

Adult Dose

1 to 2 mL (25 to 50 mg of each component) per single injection, and the lowest dose necessary to achieve adequate analgesia. The dosage may be repeated every 3 to 4 hours

Children 12 Years of Age and Under

0.5 mg of each component per pound of body weight, and the lowest dose necessary to achieve adequate analgesia. The dosage may be repeated every 3 to 4 hours.

2.3 Titration and Maintenance of Therapy

Titrate the dose based upon the individual patient's response to their initial dose of MEPERGAN.

Individually titrate MEPERGAN Injection to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving MEPERGAN Injection to assess the maintenance of pain control, signs and symptoms of opioid withdrawal, and other adverse reactions, as well as to reassess for the development of addiction, abuse, or misuse [*see Warnings and Precautions (5.1. 5.15)*]. Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration.

If the level of pain increases after dosage stabilization, attempt to identify the source of increased pain before increasing the MEPERGAN Injection dosage. If after increasing the dosage, unacceptable opioid-related adverse reactions are observed (including an increase in pain after a dosage increase), consider reducing the dosage *[see Warnings and Precautions (5)].* Adjust the dosage to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

2.4 Safe Reduction and Discontinuation of MEPERGAN Injection

When a patient who has been taking MEPERGAN Injection regularly and may be physically dependent no longer requires therapy with MEPERGAN Injection, taper the dose gradually, by 25% to 50% every 2 to 4 days, while regularly evaluating for signs and symptoms of withdrawal. If the patient develops these signs or symptoms, raise the dose to the previous level and taper more slowly, either by increasing the interval between decreases, decreasing the amount of change in dose, or both. Do not rapidly reduce or abruptly discontinue MEPERGAN Injection in patients who may be physically dependent on opioids [*see Warnings and Precautions (5.14), Drug Abuse and Dependence (9.3)*].

2.5 For Preoperative Medication

The usual adult dose is 2 mL (50 mg of each component) intramuscularly with or without appropriate atropine-like drug. Atropine sulfate, 0.3 to 0.4 mg, or scopolamine hydrobromide, 0.25 to 0.4 mg, in sterile solu1ion may be

mixed in the same syringe with MEPERGAN. Repeat doses of 50 mg or less of both promethazine and meperidine may be administered by either route at 3- to 4-hour intervals, as necessary. As an adjunct to local or general anesthesia, the usual dose is 2 mL (50 mg each of meperidine and promethazine).

3 DOSAGE FORMS AND STRENGTHS

Injectable, Tubex blunt point cartridge, 2 mL. Each mL contains 25 mg meperidine hydrochloride and 25 mg promethazine hydrochloride.
Injectable, multi-dose vial, 250 mg of meperidine HCl and 250 mg of promethazine HCl/10 mL (25 mg meperidine HCL and 25 mg promethazine HCl/mL)

4 CONTRAINDICATIONS

MEPERGAN Injection is contraindicated in patients with:

- Significant respiratory depression *[see Warnings and Precautions (5.2)]*
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment *[see Warnings and Precautions (5.7)]*
- Concomitant use of monoamine oxidase inhibitors (MAOIs) or within 14 days of having taken an MAOI. *[see Warnings and Precautions (5.6), Drug Interactions (7)]*
- Known or suspected gastrointestinal obstruction, including paralytic ileus *[see Warnings and Precautions (5.12)]*
- Hypersensitivity to meperidine or promethazine (e.g., anaphylaxis) *[See Adverse Reactions (6)]*

MEPERGAN Injection is also contraindicated:

- by intra-arterial injection, due to the likelihood of severe arteriospasm and the possibility of resultant gangrene *[See Warnings and Precautions (5.19)]*
- by the subcutaneous route; necrotic lesions have resulted

5 WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse, and Misuse

MEPERGAN Injection contains meperidine HCl and promethazine HCL. Meperidine is a Schedule II controlled substance. As an opioid, MEPERGAN Injection exposes users to the risks of addiction, abuse, and misuse *[see Drug Abuse and Dependence (9)]*.

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed MEPERGAN Injection. Addiction can occur at recommended dosages and if the drug is misused or abused. The risk of opioid-related overdose or overdose-related death is increased with higher opioid doses, and this risk persists over the course of therapy. In postmarketing studies, addiction, abuse misuse and fatal and non-fatal opioid overdose were observed in patients with long-term opioid use [see *Adverse Reactions (6.2)*].

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing MEPERGAN Injection, and monitor all patients receiving MEPERGAN Injection for the development of these behaviors and conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as MEPERGAN Injection but use in such patients necessitates intensive counseling about the risks and proper use of MEPERGAN Injection along with intensive monitoring for signs of addiction, abuse, and misuse.

Opioids are sought for nonmedical use and are subject to diversion from legitimate prescribed use. Consider these risks when prescribing or dispensing MEPERGAN Injection. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity. Contact local state professional licensing board or state-controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

5.2 Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal; respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid overdose reversal agents (e.g., naloxone, nalmefene), depending on the patient's clinical status *[see Overdosage (10)]*. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of MEPERGAN Injection, the risk is greatest during the initiation of therapy or following a dosage increase.

To reduce the risk of respiratory depression, proper dosing and titration of MEPERGAN Injection are essential *[see Dosage and Administration (2)]*. Overestimating the MEPERGAN Injection dosage when converting patients from another opioid product can result in a fatal overdose with the first dose.

Opioids can cause sleep-related breathing disorders including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper *[see Dosage and Administration (2.4)]*.

5.3 Risk from Concomitant Use with Benzodiazepines or Other CNS Depressants

The sedative action of promethazine hydrochloride is additive to the sedative effects of central nervous system depressants; therefore, agents such as alcohol, barbiturates, and opioid analgesics should either be eliminated or given in reduced dosage in the presence of promethazine hydrochloride. When given concomitantly with promethazine hydrochloride, the dose of barbiturates should be reduced by at least one-half and the dose of analgesic depressants, such as morphine or meperidine, should be reduced by one-quarter to one-half.

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of MEPERGAN Injection with benzodiazepines and/or other CNS depressants, including alcohol (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, gabapentinoids [gabapentin or pregabalin], and other opioids). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics *[see Drug Interactions (7)]*.

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Monitor patients closely for signs and symptoms of respiratory depression and sedation.

5.4 Neonatal Opioid Withdrawal Syndrome

Use of MEPERGAN Injection for an extended period of time during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for an extended period of time of the risk of neonatal opioid withdrawal syndrome and ensure that management by neonatology experts will be available at delivery *[see Use in Specific Populations (8.1)]*.

5.5 Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

Concomitant use of MEPERGAN Injection with a CYP3A4 inhibitor, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may increase plasma concentrations of meperidine and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression [*see Warnings and Precautions (5.4)*], particularly when an inhibitor is added after a stable dose of MEPERGAN Injection is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in MEPERGAN Injection-treated patients may increase meperidine plasma concentrations and prolong opioid adverse reactions. When using MEPERGAN Injection with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in MEPERGAN Injection-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of MEPERGAN Injection until stable drug effects are achieved [*Drug Interactions (7)*].

Concomitant use of MEPERGAN Injection with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease meperidine plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to meperidine. When using MEPERGAN Injection with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur [*see Drug Interactions (7)*].

5.6 Fatal Interaction with Monoamine Oxidase Inhibitors

Meperidine is contraindicated in patients who are receiving monoamine oxidase (MAO) inhibitors or those who have recently received such agents. Therapeutic doses of meperidine have occasionally precipitated unpredictable, severe, and occasionally fatal reactions in patients who have received such agents within 14 days. The mechanism of these reactions is unclear but may be related to a preexisting hyperphenylalaninemia. Some have been characterized by coma, severe respiratory depression, cyanosis, and hypotension, and have resembled the syndrome of acute opioid overdose. Serotonin syndrome with agitation, hyperthermia, diarrhea, tachycardia, sweating, tremors, and impaired consciousness may also occur. In other reactions the predominant manifestations have been hyperexcitability, convulsions, tachycardia, hyperpyrexia, and hypertension.

Do not use MEPERGAN Injection in patients taking MAOIs or within 14 days of stopping such treatment.

Intravenous hydrocortisone or prednisolone have been used to treat severe reactions, with the addition of intravenous chlorpromazine in those cases exhibiting hypertension and hyperpyrexia. The usefulness and safety of opioid overdose reversal agents in the treatment of these reactions is unknown.

5.7 Opioid-Induced Hyperalgesia and Allodynia

Opioid-Induced Hyperalgesia (OIH) occurs when an opioid analgesic paradoxically causes an increase in pain, or an increase in sensitivity to pain. This condition differs from tolerance, which is the need for increasing doses of opioids to maintain a defined effect [see *Dependence (9.3)*]. Symptoms of OIH include (but may not be limited to) increased levels of pain upon opioid dosage increase, decreased levels of pain upon opioid dosage decrease, or pain from ordinarily non-painful stimuli (allodynia). These symptoms may suggest OIH only if there is no evidence of underlying disease progression, opioid tolerance, opioid withdrawal, or addictive behavior.

Cases of OIH have been reported, both with short-term and longer-term use of opioid analgesics. Though the mechanism of OIH is not fully understood, multiple biochemical pathways have been implicated. Medical literature suggests a strong biological plausibility between opioid analgesics and OIH and allodynia. If a patient is suspected to be experiencing OIH, carefully consider appropriately decreasing the dose of the current opioid analgesic or opioid rotation (safely switching the patient to a different opioid moiety) [*see Dosage and Administration (2), Warnings and Precautions* (5.2)].

5.8 Serotonin Syndrome with Concomitant Use of Serotonergic Drugs

Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of MEPERGAN Injection with serotonergic drugs. Serotonergic drugs include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-

HT3 receptor antagonists, drugs that affect the serotonergic neurotransmitter system (e.g., mirtazapine, trazadone, tramadol), certain muscle relaxants (i.e., cyclobenzaprine, metaxalone),and drugs that impair metabolism of serotonin (including MAO inhibitors, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue) *[see Drug Interactions (7)]*. This may occur within the recommended dosage range.

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea) and can be fatal. The onset of symptoms generally occurs within several hours to a few days of concomitant use but may occur later than that. Discontinue MEPERGAN Injection if serotonin syndrome is suspected.

5.9 Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

The use of MEPERGAN Injection in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients with Chronic Pulmonary Disease: MEPERGAN Injection-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended doses of MEPERGAN Injection *[see Warnings and Precautions (5.2)]*.

Elderly, Cachectic, or Debilitated Patients*:* Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients *[see Warnings and Precautions (5.2)]*.

Monitor such patients closely, particularly when initiating and titrating MEPERGAN Injection and when MEPERGAN Injection is given concomitantly with other drugs that depress respiration *[see Warnings and Precautions (5.2, 5.3), Drug Interactions (7)]*. Alternatively, consider the use of non-opioid analgesics in these patients.

5.10 Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

5.11 Severe Hypotension

MEPERGAN Injection may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g., phenothiazines or general anesthetics) *[see Drug Interactions (7)]*. Monitor these patients for signs of hypotension after initiating or titrating the dosage of MEPERGAN Injection. In patients with circulatory shock, MEPERGAN Injection may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of MEPERGAN Injection in patients with circulatory shock.

5.12 Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

In patients who may be susceptible to the intracranial effects of CO_2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors), MEPERGAN Injection may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with MEPERGAN Injection.

Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of MEPERGAN Injection in patients with impaired consciousness or coma.

5.13 Risks of Gastrointestinal Complications

MEPERGAN Injection is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.

The meperidine HCl in MEPERGAN Injection may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

Cases of opioid-induced esophageal dysfunction (OIED) have been reported in patients taking opioids. The risk of OIED may increase as the dose and/or duration of opioids increases. Regularly evaluate patients for signs and symptoms if OIED (e.g., dysphagia, regurgitation, non-cardiac chest pain) and, if necessary, adjust opioid therapy as clinically appropriate *[see Clinical Pharmacology (12.2)]*.

5.14 Seizures

Meperidine may increase the risk of having a seizure in patients with or without a pre-existing seizure disorder. Prolonged use of meperidine may also increase the risk of seizure due to accumulation of the meperidine metabolite, normeperidine.

Frequently reevaluate patients with a history of seizure disorder for worsening seizure control and advise patients and caregivers to get emergency medical help right away in the event of a known or suspected seizure.

5.15 Withdrawal

Avoid the use of mixed agonist/antagonist (e.g., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., buprenorphine) analgesics in patients who are receiving a full opioid agonist analgesic, including MEPERGAN Injection. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or precipitate withdrawal symptoms *[see Drug Interactions (7)]*.

When discontinuing MEPERGAN Injection, gradually taper the dosage *[see Dosage and Administration (2.4)]*. Do not rapidly reduce or abruptly discontinue MEPERGAN Injection *[see Drug Abuse and Dependence (9.3)]*.

5.16 Risk of Driving and Operating Machinery

MEPERGAN Injection may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of MEPERGAN Injection and know how they will react to the medication.

5.17 Risks in Patients with Pheochromocytoma

In patients with pheochromocytoma, meperidine has been reported to provoke hypertension

5.18 Risk of Use in Patients with Atrial Flutter and Other Supraventricular Tachycardias

MEPERGAN Injection should be used with caution in patients with atrial flutter and other supraventricular tachycardias because of a possible vagolytic action which may produce a significant increase in the ventricular response rate.

5.19 Sulfite Sensitivity

MEPERGAN Injection contains sodium metabisulfite, a sulfite that may cause allergic-type reactions, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes, in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

5.20 Inadvertent Intra-Arterial Injection

Due to the close proximity of arteries and veins in the areas most commonly used for intravenous injection, extreme care should be exercised to avoid perivascular extravasation or inadvertent intra-arterial injection of MEPERGAN.

Reports compatible with inadvertent intra-arterial injection suggest that pain, severe chemical irritation, severe spasm of distal vessels, and resultant gangrene requiring amputation is likely under such circumstances. Intravenous injection was intended in all the cases reported, but perivascular extravasation or arterial placement of the needle is now suspect. There is no proven successful management of this condition after it occurs, although sympathetic block and heparinization are commonly employed during the acute management because of the results of animal experiments with other known arteriolar irritants. Aspiration of dark blood does not preclude intra-arterial needle placement, because blood is discolored upon contact with promethazine. Use of syringes with rigid plungers or of small bore needles might obscure typical arterial backflow if this is relied upon alone.

5.21 Intravenous Use

If necessary, MEPERGAN Injection may be given intravenously, but the injection should be given very slowly, preferably in the form of a diluted solution. Rapid intravenous injection of MEPERGAN Injection, increases the incidence of adverse reactions; severe respiratory depression, apnea, hypotension, peripheral circulatory collapse, and cardiac arrest have occurred. MEPERGAN Injection should not be administered intravenously unless an opioid overdose reversal agent and the facilities for assisted or controlled respiration are immediately available. When MEPERGAN Injection is given parenterally, especially intravenously, the patient should be lying down.

When used intravenously, MEPERGAN Injection should be given at a rate not to exceed 1 mL (25 mg of each component) per minute. When administering any irritant drug intravenously, it is usually preferable to inject it through the tubing of an intravenous infusion set that is known to be functioning satisfactorily. In the event that a patient complains of pain during intended intravenous injection of MEPERGAN, the injection should immediately be stopped to provide for evaluation of possible arterial placement or perivascular extravasation.

5.22 Laboratory Tests

In patients receiving promethazine, diagnostic pregnancy tests based on immunological reactions between HCG and anti-HCG may result in false negative or false positive results.

Glucose tolerance may appear increased during glucose tolerance te4sts in patients receiving promethazine.

6 ADVERSE REACTIONS

The following serious adverse reactions are described, or described in greater detail, in other sections:

- Addiction, Abuse, and Misuse *[see Warnings and Precautions (5.1)]*
- Life-Threatening Respiratory Depression *[see Warnings and Precautions (5.2)]*
- Interactions with Benzodiazepines or Other CNS Depressants *[see Warnings and Precautions (5.3)]*
- Neonatal Opioid Withdrawal Syndrome *[see Warnings and Precautions (5.4)]*
- Opioid-Induced Hyperalgesia and Allodynia *[see Warnings and Precautions (5.7)*
- Serotonin Syndrome *[see Warnings and Precautions (5.9)]*
- Adrenal Insufficiency *[see Warnings and Precautions (5.10)]*
- Severe Hypotension *[see Warnings and Precautions (5.11)]*
- Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.13)]*
- Seizures *[see Warnings and Precautions (5.14)]*
- Withdrawal *[see Warnings and Precautions (5.15)]*

The following adverse reactions associated with the use of meperidine were identified in clinical studies or postmarketing reports. Because some of these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The major hazards of meperidine, as with other opioid analgesics, are respiratory depression and, to a lesser degree, circulatory depression; respiratory arrest, shock, and cardiac arrest.

The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea, vomiting, and sweating. These effects seem to be more prominent in ambulatory patients and in those who are not experiencing severe pain. In such individuals, lower doses are advisable. Some adverse reactions in ambulatory patients may be alleviated if the patient lies down.

Other adverse reactions include:

Central Nervous System: Euphoria, dysphoria, weakness, headache, agitation, tremor, uncoordinated muscle movements, seizures, transient hallucinations and disorientation, visual disturbances and, rarely, extrapyramidal reactions.

Gastrointestinal: Dry mouth, constipation, biliary-tract spasm.

Cardiovascular: Flushing of the face, tachycardia, bradycardia, palpitation, faintness, syncope, increased blood pressure, decreased blood pressure

Venous thrombosis at the injection site has been reported. Intra-arterial injection of MEPERGAN may result in gangrene of the affected extremity.

Genitourinary: Urinary retention.

Allergic: Pruritus, urticaria, other skin rashes, wheal and flare over the vein with IV injection, photosensitivity.

Photosensitivity, although extremely rare, has been reported. Occurrence of photosensitivity may be a contraindication to further treatment with promethazine or related drugs.

Other: Pain at injection site; local tissue irritation, induration, and possible tissue necrosis, particularly when injection is repeated at same site; antidiuretic effect.

Patients may occasionally complain of autonomic reactions, such as dryness of the mouth, blurring of vision and, rarely, dizziness following the use of promethazine.

Very rare cases have been reported where patients receiving promethazine have developed leukopenia. In one instance agranulocytosis has been reported. In nearly every instance reported, other toxic agents known to have caused these conditions have been associated with the administration of promethazine.

Serotonin syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.

Adrenal insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.

Anaphylaxis: Anaphylaxis has been reported with ingredients contained in MEPERGAN Injection.

Androgen deficiency: Cases of androgen deficiency have occurred with use of opioids for an extended period of time *[see Clinical Pharmacology (12.2)]*.

Hyperalgesia and Allodynia: Cases of hyperalgesia and allodynia have been reported with opioid therapy of any duration [*see Warnings and Precautions (5.7)*].

Hypoglycemia: Cases of hypoglycemia have been reported in patients taking opioids. Most reports were in patients with at least one predisposing risk factor (e.g., diabetes).

Opioid-Induced esophageal dysfunction (OIED): Cases of OIED have been reported in patients taking higher opioids and may occur more frequently in patients taking higher doses of opioids, and/or in patients taking opioids longer term *[see Warnings and Precautions (5.13)]*.

Adverse Reactions from Observational Studies

A prospective, observational cohort study estimated the risks of addiction, abuse, and misuse in patients initiating long-term use of Schedule II opioid analgesics between 2017 and 2021. Study participants included in one or more analyses had been enrolled in selected insurance plans or health systems for at least one year, were free of at least one outcome at baseline, completed a minimum number of follow-up assessments, and either: 1) filled multiple extended-release/long-acting opioid analgesic prescriptions during a 90-day period (n=978); or 2) filled any Schedule II opioid analgesic prescriptions covering at least 70 of 90 days (n=1,244). Those included also had no dispensing of the qualifying opioids in the previous 6 months.

Over 12 months:

- approximately 1% to 6% of participants across the two cohorts newly met criteria for addiction, as assessed with two validated interview-based measures of moderate-to-severe opioid use disorder based on Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria, and
- approximately 9% and 22% of participants across the two cohorts newly met criteria for prescription opioid abuse and misuse *[defined in Drug Abuse and Dependence (9.2)]*, respectively, as measured with a validated self-reported instrument.

A retrospective, observational cohort study estimated the risk of opioid involved overdose or opioid overdose-related death in patients with new long-term use of Schedule II opioid analgesics from 2006 through 2016 (n=220,249). Included patients had been enrolled in either one of two commercial insurance programs, one managed care program, or one Medicaid program for at least 9 months. *New long-term use* was defined as having Schedule II opioid analgesic prescriptions covering at least 70 days' supply over the 3 months prior to study entry and none during the preceding 6 months. Patients were excluded if they had an opioid-involved overdose in the 9 months prior to study entry. Overdose was measured using a validated medical code-based algorithm with linkage to the National Death Index database. The 5-year cumulative incidence estimates for opioid-involved overdose or opioid overdose-related death ranged from approximately 1.5% to 4% across study sites, counting only the first event during follow-up. Approximately 17% of first opioid overdoses observed over the entire study period (5-11 years, depending on the study site) were fatal. Higher baseline opioid dose was the strongest and most consistent predictor of opioid-involved overdose or opioid overdose-related death. Study exclusion criteria may have selected patients at lower risk of overdose, and substantial loss to follow-up (approximately 80%) also may have biased estimates. The risk estimates from the studies described above may not be generalizable to all patients receiving opioid analgesics, such as those with exposures shorter or longer than the duration evaluated in the studies.

7 DRUG INTERACTIONS

The table below includes clinically significant drug interactions with MEPERGAN Injection.

Clinically Significant Drug Interactions with MEPERGAN Injection	
Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact:	Meperidine is contraindicated in patients who are receiving monoamine oxidase (MAO) inhibitors or those who have recently received such agents. Therapeutic doses of meperidine have occasionally precipitated unpredictable, severe, and occasionally fatal reactions in patients who have received such agents within 14 days. The mechanism of these reactions is unclear but may be related to a preexisting hyperphenylalaninemia. Some have been characterized by coma, severe respiratory depression, cyanosis, and

	hypotension, and have resembled the syndrome of acute opioid overdose. Serotonin syndrome with agitation, hyperthermia, diarrhea, tachycardia, sweating, tremors, and impaired consciousness may also occur. In other reactions the predominant manifestations have been hyperexcitability, convulsions, tachycardia, hyperpyrexia, and hypertension. *[See Warnings and Precautions (5.6)]*
Intervention:	Do not use MEPERGAN Injection in patients taking MAOIs or within 14 days of stopping such treatment. Intravenous hydrocortisone or prednisolone have been used to treat severe reactions, with the addition of intravenous chlorpromazine in those cases exhibiting hypertension and hyperpyrexia. The usefulness and safety of opioid overdose reversal agents in the treatment of these reactions are unknown.
Examples:	phenelzine, tranylcypromine, linezolid
Inhibitors of CYP3A4 and CYP2B6	
Clinical Impact:	The concomitant use of MEPERGAN Injection and CYP3A4 or CYP2B6 inhibitors can increase the plasma concentration of meperidine, resulting in increased or prolonged opioid effects. These effects could be more pronounced with concomitant use of MEPERGAN Injection and CYP2B6 and CYP3A4 inhibitors, particularly when an inhibitor is added after a stable dose of MEPERGAN Injection is achieved [*see Warnings and Precautions (5.4)*]. After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the meperidine plasma concentration will decrease [*see Clinical Pharmacology (12.3)*], potentially resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to meperidine.
Intervention:	If concomitant use is necessary, consider dosage reduction of MEPERGAN Injection until stable drug effects are achieved. Evaluate patients at frequent intervals for respiratory depression and sedation. If a CYP3A4 or CYP2B6 inhibitor is discontinued, consider increasing the MEPERGAN Injection dosage until stable drug effects are achieved. Assess for signs of opioid withdrawal.
Examples:	Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), protease inhibitors (e.g., ritonavir)
CYP3A4 and CYP2B6 Inducers	
Clinical Impact:	The concomitant use of MEPERGAN Injection and CYP3A4 inducers, or CYP2B6 inducers can decrease the plasma concentration of meperidine [*see Clinical Pharmacology (12.3)*], resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to meperidine [*see Warnings and Precautions (5.4)*]. After stopping a CYP3A4 or CYP2B6 inducer, as the effects of the inducer decline, the meperidine plasma concentration will increase [*see Clinical Pharmacology (12.3)*], which could increase or prolong both the therapeutic effects and adverse reactions and may cause serious respiratory depression.
Intervention:	If concomitant use is necessary, consider increasing the MEPERGAN Injection dosage until stable drug effects are achieved. Assess for signs of opioid withdrawal. If a CYP3A4 or CYP2B6 inducer is discontinued, consider MEPERGAN Injection dosage reduction and monitor for signs of respiratory depression.
Examples:	Rifampin, carbamazepine, phenytoin
Benzodiazepine and Other Central Nervous System (CNS) Depressants	

Clinical Impact:	Due to the additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death *[see Warnings and Precautions (5.3)]*.
Intervention:	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Monitor closely for signs of respiratory depression and sedation *[see Warnings and Precautions (5.3)]*.
Examples:	Benzodiazepines and other sedatives/hypnotics, anxiolytics, barbiturates, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, gabapentinoids (gabapentin or pregabalin), other opioids, alcohol.
Serotonergic Drugs	
Clinical Impact:	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome *[see Warnings and Precautions (5.8)]*.
Intervention:	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue MEPERGAN Injection if serotonin syndrome is suspected.
Examples:	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (i.e., cyclobenzaprine, metaxalone), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).
Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics	
Clinical Impact:	May reduce the analgesic effect of MEPERGAN Injection and/or precipitate withdrawal symptoms.
Intervention:	Avoid concomitant use.
Examples:	Butorphanol, nalbuphine, pentazocine, buprenorphine.
Muscle Relaxants	
Clinical Impact:	Meperidine may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
Intervention:	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of MEPERGAN Injection and/or the muscle relaxant as necessary.
Examples:	Cyclobenzaprine, metaxalone.
Diuretics	
Clinical Impact:	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
Intervention:	Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Anticholinergic Drugs	
Clinical Impact:	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Intervention:	Monitor patients for signs of urinary retention or reduced gastric motility when MEPERGAN Injection is used concomitantly with anticholinergic drugs.
Acyclovir	
Clinical Impact:	The concomitant use of acyclovir may increase the plasma concentrations of meperidine and its metabolite, normeperidine.
Intervention:	If concomitant use of acyclovir and MEPERGAN Injection is necessary, monitor patients for respiratory depression and sedation at frequent intervals.
Cimetidine	

Clinical Impact:	The concomitant use of cimetidine may reduce the clearance and volume of distribution of meperidine also the formation of the metabolite, normeperidine, in healthy subjects
Intervention:	If concomitant use cimetidine and MEPERGAN Injection is necessary, monitor patients for respiratory depression and sedation at frequent intervals.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Use of opioid analgesics for an extended period of time during pregnancy may cause neonatal opioid withdrawal syndrome *[see Warnings and Precautions (5.4)]*. Available data with MEPERGAN Injection in pregnant women are insufficient to inform a drug-associated risk for major birth defects and miscarriage or adverse maternal outcomes. There are adverse outcomes reported with fetal exposure to opioid analgesics (*see Clinical Considerations*).

Formal animal reproduction studies have not been conducted with meperidine, promethazine, or the combination. Neural tube defects (exencephaly and cranioschisis) have been reported in hamsters administered a single bolus dose of meperidine during a critical period of organogenesis at 2.6 and 4.4 times the total human daily dose of 400 mg meperidine hydrochloride. Increased resorptions of fetuses in pregnant mice and rats and skeletal fragility, decreased pup weight, and developmental delays were reported in rat pups born to dams treated with promethazine during gestation at doses within the human dosing range during gestation have been reported [*see Data*].

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions
Use of opioid analgesics for an extended period of time during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea, and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn. Observe newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly *[see Warnings and Precautions (5.3)]*.

Labor or Delivery
Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid overdose reversal agent, such as naloxone or nalmefene, must be available for reversal of opioid-induced respiratory depression in the neonate. MEPERGAN Injection is not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate. Opioid analgesics, including MEPERGAN Injection, can prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

Data

Animal Data

Formal reproductive and developmental toxicology studies for meperidine, promethazine, or the combination have not been completed.

In a published study, neural tube defects (exencephaly and cranioschisis) were noted following subcutaneous administration of meperidine hydrochloride (127 and 218 mg/kg, respectively) on Gestation Day 8 to pregnant

hamsters (2.6 and 4.4 times the total daily dose of 400 mg meperidine hydrochloride/day based on body surface area). The findings cannot be clearly attributed to maternal toxicity.

No evidence of embryotoxicity or malformations were reported in a published study in which pregnant rats were treated with promethazine hydrochloride from Gestation Day 1 to 15 or 10 through 15 via oral gavage doses of 50 to 250 mg/kg/day (1.2 to 6.1 times the HDD of 400 mg/day based on body surface area).

Increased resorptions were reported in a published study in which pregnant rats were treated orally from Gestation Day 5 to 16 with 20 mg/kg promethazine hydrochloride (0.5 times the human daily dose of 400 mg). Increased resorptions were reported in a second published study in which pregnant mice were treated intraperitoneally from Gestation Day 1 to 5 with 1 mg/kg promethazine hydrochloride (0.01 times the human daily dose of 400 mg based on body surface area).

Skeletal fragility of pups was reported in a published study in which pregnant Lister Hooded rats were treated orally from Gestation Day 7 to 13 with 5 or 10 mg/kg promethazine hydrochloride (0.12 or 0.24 times the human daily dose of 400 mg based on body surface area). No malformations or maternal toxicity were reported. Subsequent studies suggested that the effect was most prominent when treated on Days 10 to 12 of gestation.

Decreased pup weight and delays in initial occurrence of behavioral/reflex responses in pups were reported in a published study in which pregnant rats were treated orally from Gestation Day 10 to 12 with 10 mg/kg promethazine hydrochloride (0.24 times the human daily dose of 400 mg based on body surface area).

8.2 Lactation

Risk Summary

Meperidine appears in the milk of nursing mothers receiving the drug. Promethazine can inhibit prolactin release and therefore may interfere with lactation.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for MEPERGAN Injection and any potential adverse effects on the breastfed infant from MEPERGAN Injection or from the underlying maternal condition.

Clinical Considerations

Monitor infants exposed to MEPERGAN Injection through breast milk for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

8.3 Females and Males of Reproductive Potential

Infertility

Use of opioids for an extended period of time may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible *[see Adverse Reactions (6), Clinical Pharmacology (12.2)], Nonclinical Pharmacology (13.1)]*.

8.4 Pediatric Use

The safety and efficacy of MEPERGAN Injection in pediatric patients has not been established.

8.5 Geriatric Use

Elderly patients (aged 65 years or older) may have increased sensitivity to meperidine. In general, use caution when selecting a dosage for an elderly patient, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

Respiratory depression is the chief risk for elderly patients treated with opioids and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of MEPERGAN Injection slowly in geriatric patients and monitor for signs of central nervous system and respiratory depression *[see Warnings and Precautions (5.9)]*.

Meperidine and promethazine are known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more

likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

8.6 Hepatic Impairment

Accumulation of meperidine and/or its active metabolite, normeperidine, can occur in patients with hepatic impairment. Elevated serum levels have been reported to cause central nervous system excitatory effects. Meperidine should therefore be used with caution in patients with hepatic impairment. Titrate the dosage of MEPERGAN Injection slowly in patients with renal impairment and monitor closely for signs of central nervous system and respiratory depression.

8.7 Renal Impairment

Accumulation of meperidine and/or its active metabolite, normeperidine, can also occur in patients with renal impairment. Meperidine should therefore be used with caution in patients with renal impairment. Titrate the dosage of MEPERGAN Injection slowly in patients with renal impairment and monitor closely for signs of central nervous system and respiratory depression.

8.8 Special Risk Patients

Antiemetics such as promethazine may mask the symptoms of an unrecognized disease and thereby interfere with diagnosis.

Patients in pain who have received inadequate or no analgesia have been noted to develop "athetoid-like" movements of the upper extremities following the parenteral administration of promethazine. These symptoms usually disappear upon adequate control of the pain.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

MEPERGAN Injection contains meperidine, a Schedule II controlled drug substance.

9.2 Abuse

MEPERGAN Injection contains meperidine, a substance with a high potential for misuse and abuse which can lead to the development of substance use disorder, including addiction *[see Warnings and Precautions (5.1)]*.

Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by healthcare provider or for whom it was not prescribed.

Abuse is the intentional, non-therapeutic use of a drug, even once, for its desirable psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use (e.g., continuing drug use despite harmful consequences, giving a higher priority to drug use than other activities and obligations), and possible tolerance or physical dependence.

Misuse and abuse of MEPERGAN Injection increases risk of overdose, which may lead to central nervous system and respiratory depression, hypotension, seizures and death. The risk is increased with concurrent abuse of MEPERGAN with alcohol and/or other CNS depressants. Abuse of and addiction to opioids in some individuals may not be accompanied by concurrent tolerance and symptoms of physical dependence. In addition, abuse of opioids can occur in the absence of addiction.

All patients treated with opioids require careful and frequent reevaluation for signs of misuse, abuse, and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use. Patients at high risk of MEPERGAN Injection abuse include those with a history of prolonged use of any opioid, including products containing meperidine, those with a history of drug or alcohol abuse, or those who use MEPERGAN Injection in combination with other abused drugs.

"Drug-seeking" behavior is very common in persons with substance use disorders. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing, or referral, repeated "loss" of prescriptions, tampering with prescriptions, and reluctance to provide prior medical records or contact information for other treating healthcare provider(s). "Doctor shopping" (visiting multiple prescribers to obtain additional prescriptions) is common among people with substance use disorder. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with inadequate pain control.

MEPERGAN Injection, like other opioids, can be diverted for nonmedical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state and federal law, is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic reevaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Risks Specific to Abuse of MEPERGAN Injection

Abuse of MEPERGAN Injection poses a risk of overdose and death. The risk is increased with concurrent abuse of MEPERGAN Injection with alcohol and/or other CNS depressants.

Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

9.3 Dependence

Both tolerance and physical dependence can develop during use of opioid therapy.

Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose).

Physical dependence is a state that develops as a result of a physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or significant dose reduction of a drug.

Withdrawal may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene), mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued use.

MEPERGAN Injection should not be rapidly reduced or abruptly discontinued in a physically-dependent patient *[see Dosage and Administration (2)]*. If MEPERGAN is rapidly reduced or abruptly discontinued in a physically-dependent patient, a withdrawal syndrome may occur, typically characterized by restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs *[see Use in Specific Populations (8.1)]*.

10 OVERDOSAGE

Clinical Presentation

Acute overdose with meperidine can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases, pulmonary edema, bradycardia, hypotension, hypoglycemia, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations *[See Clinical Pharmacology (12.2)]*. Toxic leukoencephalopathy has been reported after opioid overdose and can present hours, days or weeks after apparent recovery from the initial intoxication.

Accumulation of normeperidine as in chronic use or possibly following introduction of a concomitant CYP3A4 inducer presents as excitatory syndrome including hallucinations, tremors, muscle twitches, dilated pupils, hyperactive reflexes, and convulsions.

Treatment of Overdose

In case of overdose, priorities are the reestablishment of a patent and protected airway and institution of assisted or controlled ventilation, if needed. Employ other supportive measured (including oxygen and vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life-support measures.

For clinically significant respiratory or circulatory depression secondary to meperidine overdose, administer an opioid overdose reversal agent such as naloxone or nalmefene.

Because the duration of opioid reversal is expected to be less than the duration of action of meperidine in MEPERGAN Injection, carefully monitor the patient until spontaneous respiration is reliably reestablished. If the response to an opioid overdose reversal agent is suboptimal or only brief in nature, administer additional reversal agent as directed by the product's prescribing information.

In an individual physically dependent on opioids, administration of the recommended usual dosage of the opioid overdose reversal agent will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the reversal agent administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the reversal agent should be initiated with care and by titration with smaller than usual doses of the reversal agent.

Attempted suicides with promethazine have resulted in deep sedation, coma, rarely convulsions and cardiorespiratory symptoms compatible with the depth of sedation present. Extrapyramidal reactions may be treated with anticholinergic antiparkinson agents, diphenhydramine, or barbiturates.

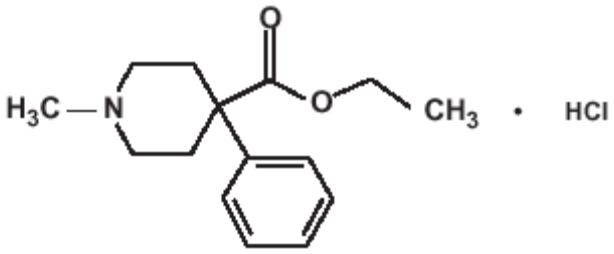
If severe hypotension occurs, levarterenol or phenylephrine may be indicated. Avoid epinephrine as promethazine overdosage could produce a partial alpha-adrenergic blockade.

A paradoxical reaction, characterized by hyperexcitability and nightmares, has been reported in children receiving large single doses of promethazine.

11 DESCRIPTION

MEPERGAN Injection is a combination product containing meperidine HCl, an opioid agonist, and promethazine HCl, a phenothiazine, for intramuscular and intravenous use. Meperidine hydrochloride is an opioid agonist. with multiple actions qualitatively similar to those of morphine. Promethazine hydrochloride) is a phenothiazine derivative that has several different pharmacologic properties, including antihistaminic, sedative, and antiemetic actions.

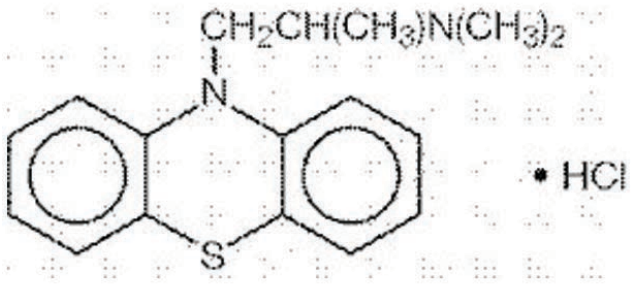
The chemical name for meperidine hydrochloride is 4-Piperidinecarboxylic acid, 1-methyl-4-phenyl-,ethyl ester, hydrochloride. The molecular weight is 283,80. Its molecular formula is $C_{15}H_{21}NO_2 \cdot HCl$, and it has the following chemical structure.



Meperidine hydrochloride is a white crystalline substance with a melting point of 186° C to 189° C. It is readily soluble in water and has a neutral reaction and a slightly bitter taste. The solution is not decomposed by a short period of boiling.

Promethazine HCl is a racemic compound; the empirical formula is C17H20N2S•HCl and its molecular weight is 320.88.

Promethazine HCl, a phenothiazine derivative, is designated chemically as 10*H*-Phenothiazine-10-ethanamine, *N,N,*□-trimethyl-, monohydrochloride, (±)- with the following structural formula::



Promethazine hydrochloride occurs as a white to faint yellow, practically odorless, crystalline powder which slowly oxidizes and turns blue on prolonged exposure to air. It is soluble in water and freely soluble in alcohol.

MEPERGAN Injection provides 25 mg each of meperidine hydrochloride and promethazine hydrochloride per mL with 0.1 mg edetate disodium, 0.04 mg calcium chloride, and not more than 0.75 mg sodium formaldehyde sulfoxylate, 0.25 mg sodium metabisulfite, and 5 mg phenol with sodium acetate buffer.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Meperidine hydrochloride is an opioid agonist. Promethazine, a phenothiazine, is believed to primarily function as a histamine H1 receptor antagonist, muscarinic antagonist, and dopamine D2 receptor antagonist.

12.2 Pharmacodynamics

Effects on the Central Nervous System

Meperidine produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centers to both increases in carbon dioxide tension and electrical stimulation.

Meperidine causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomic (e.g., pontine lesions of hemorrhagic or ischemic origins may produce similar findings). Marked mydriasis rather than miosis may be seen due to hypoxia in overdose situations.

Effects on the Gastrointestinal Tract and Other Smooth Muscle

Meperidine causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm, resulting in constipation. Other opioid-induced effects may include a reduction in biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase, and opioid-induced esophageal dysfunction (OIED).

Effects on the Cardiovascular System

Meperidine produces peripheral vasodilation which may result in orthostatic hypotension or syncope. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Effects on the Endocrine System

Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and lutenizing hormone (LH) in humans *[See Adverse Reactions (6)]*. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon *[See Adverse Reactions (6)]*.

Use of opioids for an extended period of time may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date *[see Adverse Reactions (6)]*.

Effects on the Immune System

Opioids have been shown to have a variety of effects on components of the immune system in *in vitro* and animal models. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

Concentration – Efficacy Relationships

The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with opioid agonists. The minimum effective analgesic concentration of meperidine for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome, and/or the development of analgesic tolerance *[See Dosage and Administration (2.1, 2.3)]*.

Concentration – Adverse Reaction Relationships

There is a relationship between increasing meperidine plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions *[See Dosage and Administration (2.1, 2.3)]*.

12.3 Pharmacokinetics

Meperidine

Elimination
The elimination half-life of meperidine is 3 to 8 hours in healthy volunteers. The only bioactive metabolite of meperidine is normeperidine which has an average elimination half-life of 20.6 hours.

Metabolism
Meperidine is metabolized through biotransformation. *In vitro* data show meperidine is metabolized to normeperidine in liver mainly by CYP3A4 and CYP2B6.

Excretion
Meperidine and normeperidine are excreted by kidneys.

Age
In clinical studies reported in the literature, changes in several meperidine pharmacokinetic parameters with increasing age have been observed. The initial volume of distribution and steady-state volume of distribution of meperidine may be higher in elderly patients than in younger patients. The free fraction of meperidine in plasma may be higher in patients over 45 years of age than in younger patients.

Hepatic impairment
The elimination half-life of meperidine is 3 to 8 hours in healthy volunteers and is 1.3 to 2 times greater in post-operative or cirrhotic patients.

Promethazine

Elimination

Promethazine is metabolized by the liver and its metabolites can be found in urine.

Metabolism
Promethazine is metabolized by the liver to a variety of compounds.

Excretion
The sulfoxides of promethazine and N-demethylpromethazine are the predominant metabolites appearing in the urine.

Drug Interactions Studies with Meperidine

Phenytoin
The hepatic metabolism of meperidine may be enhanced by phenytoin. Concomitant administration resulted in reduced half-life and bioavailability with increased clearance of meperidine in healthy subjects; however, blood concentrations of normeperidine were increased (*See Drug Interactions, 7*).

Ritonavir
Plasma concentrations of the active metabolite normeperidine may be increased by ritonavir (*See Drug Interactions, 7*).

Acyclovir
Plasma concentrations of meperidine and its metabolite, normeperidine, may be increased by acyclovir (*See Drug Interactions, 7*).

Cimetidine
Cimetidine reduced the clearance and volume of distribution of meperidine and also the formation of the metabolite, normeperidine, in healthy subjects (*See Drug Interactions, 7*).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
No evidence of carcinogenic potential was noted in long-term studies in rats and mice treated with oral promethazine hydrochloride doses up to 33 and 45 mg/kg (0.8 and 0.5 times the maximum human daily dose of 400 mg/day on a mg/m^2 basis, respectively).

Long-term studies in animals to evaluate the carcinogenic potential of meperidine have not been conducted.

Mutagenesis
Promethazine tested positive in the presence of a metabolic activator (S9 mix) and negative in the absence of it in the in vitro sister chromatid exchange assay. Negative results were reported in the in vitro bacterial reverse mutation assay and the in vitro chromosome aberration assay.

Studies to assess the mutagenic potential of meperidine have not been conducted.

Impairment of Fertility
Studies in animals to determine the effect of meperidine or promethazine on fertility have not been conducted.

16 HOW SUPPLIED/STORAGE AND HANDLING

MEPERGAN (meperidine HCI and promethazine HCI) Injection is available in TUBEX® BLUNT POINTETM Sterile Cartridge Units and Sterile Cartridge-Needle Units, in boxes of 10 TUBEX in TAMP-R-TEL® tamper-resistant packages as follows:
NDC pending, 2 mL size Blunt PointeTM.

NDC pending, 2 mL size (22 gauge x 1-1/4 inch needle).

MEPERGAN (meperidine HCI and promethazine HCI) Injection is also available in vials as follows:

NDC pending, 10 mL vial.

Do not use if solution is discolored or contains a precipitate
Protect from light
Use carton to protect contents from light
Store at room temperature, approximately 25° C (77° F)

17 PATIENT COUNSELING INFORMATION

Addiction, Abuse, and Misuse

Inform patients that the use of MEPERGAN Injection, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose and death *[see Warnings and Precautions (5.1)]*.

Life-Threatening Respiratory Depression

Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting MEPERGAN Injection or when the dosage is increased, and that it can occur even at recommended dosages *[see Warnings and Precautions (5.2)]*.

Hyperalgesia and Allodynia

Advise patients to inform their healthcare provider if they experience symptoms of hyperalgesia, including worsening pain, increased sensitivity to pain, or new pain *[see Warnings and Precautions (5.7), Adverse Reactions (6)]*.

Serotonin Syndrome

Inform patients that opioids could cause a rare but potentially life-threatening condition called serotonin syndrome resulting from concomitant administration of serotonergic drugs. Warn patients of the symptoms of serotonin syndrome and to seek medical attention right away if symptoms develop after discharge from the hospital. Instruct patients to inform their healthcare provider if they are taking or plan to take serotonergic medications *[see Warnings and Precautions (5.8), Drug Interactions (7)]*.

Constipation

Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention *[see Adverse Reactions (6), Clinical Pharmacology (12.2)]*.

Manufactured by:

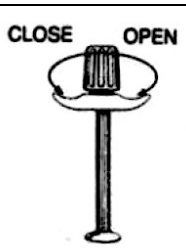
WW (logo)

WEST-WARD
A HIKMA COMPANY

Eatontown, NJ 07724 USA

1-877-845-0699

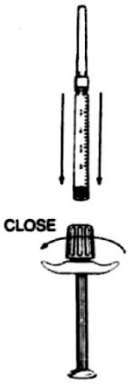
To load a DOSETTE® Sterile Cartridge-Needle Unit into the TUBEX® Injector



1. Turn the ribbed collar to the "OPEN" position until it stops.

2. Hold the Injector with the open end up and fully insert the DOSETTE® Sterile Cartridge-Needle Unit.

Firmly tighten the ribbed collar in the direction of the "CLOSE" arrow.



3. Thread the plunger rod into the plunger of the DOSETTE® Sterile Cartridge-Needle

Unit until slight resistance is felt.

4. Engage the needle-cap assembly by pulling the cap down over the silver cartridge hub. The needle is fully engaged when the silver hub is completely covered.

The Injector is now ready for use in the usual manner.

To administer TUBEX®/DOSETTE® Sterile Cartridge-Needle Units

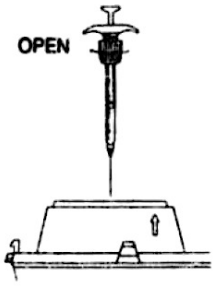
Method of administration is the same as with conventional syringe. Remove needle cover by grasping it securely; twist and pull. Introduce needle into patient, aspirate by pulling back slightly on the plunger, and inject.

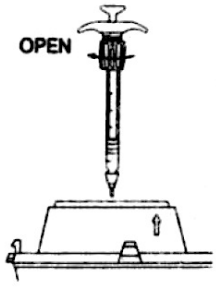
To administer TUBEX® BLUNT POINTE™ Sterile Cartridge Units

"Needle-less" IV set administration is similar to administration with conventional syringes. Remove rubber cover by grasping it securely; twist and pull. For B. Braun Medical's SafSite® Reflux Valves, aseptically swab the luer slip fitting of the BLUNT POINTE™ sterile cartridge tip assembly with a sterile, individually wrapped, saturated 70% Isopropyl Alcohol swab. This action will remove the lubricant coating from the tip to facilitate a tight seal. Introduce TUBEX® BLUNT POINTE™ Sterile Cartridge Unit into the "needle-less" IV set as per manufacturer's "Directions for Use."

To remove the empty TUBEX®/DOSETTE® Cartridge Unit and dispose into a vertical disposal container

1. Do not recap the needle/point. Disengage the plunger rod.
2. Hold the Injector, needle/point down, over a vertical disposal container and loosen the ribbed collar. TUBEX®/DOSETTE® Cartridge Unit will drop into the container.

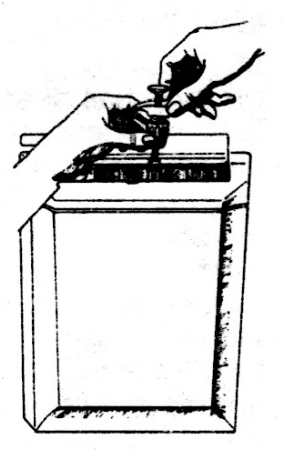




3. Discard the cover.

To remove the empty TUBEX®/DOSETTE® Cartridge Unit and dispose into a horizontal (mailbox) disposal container

1. Do not recap the needle/point. Disengage the plunger rod.



2. Open the horizontal (mailbox) disposal container. Insert TUBEX®/DOSETTE® Cartridge Unit, needle/point pointing down, halfway into container. Close the container lid on cartridge. Loosen ribbed collar; TUBEX®/DOSETTE® Cartridge Unit will drop into the container.

3. Discard the cover.

The TUBEX® Injector is reusable and should not be discarded.

Used TUBEX®/DOSETTE® Cartridge Units should not be employed for successive injections or as multiple-dose containers. They are intended to be used only once and discarded.

NOTE: Any graduated markings on TUBEX®/DOSETTE® Sterile Cartridge Units are to be used only as a guide in mixing, withdrawing, or administering measured doses.