HIGHLIGHTS OF PRESCRIBING INFORMATION

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

DEMEROL™ (meperidine hydrochloride injection), for subcutaneous, intramuscular, and intravenous use, CII

Initial U.S. Approval: 1942

WARNING: SERIOUS AND LIFE-THREATENING RISKS FROM USE OF DEMEROL INJECTION

See full prescribing information for complete boxed warning.

- **DEMEROL 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 DEMEROL Injection, especially during initiation or following a dosage increase. To reduce the risk of respiratory depression, proper dosing and titration of DEMEROL 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, 7)**
- **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. (5.4)**
- **Concomitant use with CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) can result in a fatal overdose of meperidine. (5.5, 7)**
- **Concomitant use of DEMEROL Injection with Monoamine oxidase (MAO) inhibitors can result in coma, severe respiratory depression, cyanosis and hypotension. Use of DEMEROL Injection with MAO inhibitors is contraindicated. (4, 5.6, 7)**

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

Boxed Warning	12/2025
Indications and Usage (1)	12/2025
Dosage and Administration (2.2)	12/2025
Warnings and Precautions (5.1, 5.2, 5.3, 5.13, 5.14, 5.15)	12/2025

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

DEMEROL Injection is indicated for preoperative medication, support of anesthesia, for obstetrical analgesia, and for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. (1)

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 DEMEROL 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.

Use of DEMEROL Injection for an extended period of time may increase the risk of toxicity (e.g., seizures) from the accumulation of the meperidine metabolite, normeperidine. (1, 5.1)

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

- DEMEROL 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 DEMEROL 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. (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, 5.2)
- Respiratory depression can occur at any time during opioid therapy, especially when initiating and following dosage increases with DEMEROL Injection. Consider this risk when selecting an initial dose and when making dose adjustments. (2.2, 5.3)
- Periodically reassess patients receiving DEMEROL Injection to evaluate the continued need for opioid analgesics to maintain pain control, for the signs or symptoms of adverse reactions, and for the development of addiction, abuse, or misuse. (2.2)
- For Relief of Pain:
  Titrate the dose based upon the individual patient's response to their initial dose of DEMEROL Injection. (2.2, 5)
  Adults: 50 mg to 150 mg intramuscularly or subcutaneously every 3 to 4 hours. (2.2)
  Children: 0.5 mg/lb to 0.8 mg/lb intramuscularly or subcutaneously up to the adult dose every 3 to 4 hours. (2.2)
- Preoperative Medication:
  Adults: 50 mg to 100 mg intramuscularly or subcutaneously, 30 to 90 minutes before beginning anesthesia. (2.3)
  Children: 0.5 mg/lb to 1 mg/lb intramuscularly or subcutaneously up to the adult dose, 30 to 90 minutes before beginning anesthesia. (2.3)
- Obstetrical Analgesia:
  50 mg to 100 mg intramuscularly or subcutaneously; may be repeated at 1 to 3 hour intervals. (2.4)
- Do not rapidly reduce or abruptly discontinue DEMEROL Injection in a physically-dependent patient. (2.2, 5.15)

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

- Injectable, Carpuject™ Single-dose cartridge with Luer Lock for the Carpuject Syringe System, to be used ONLY with Carpuject™ Holder: 25 mg/mL, 50 mg/mL, 75 mg/mL, and 100 mg/mL. (3)
- Injectable, Multiple-dose vials: 1,500 mg/30 mL (50 mg/mL). (3)
- Injectable, NexJect™ Single-dose Prefilled Syringe with Luer Lock: 25 mg/mL and 50 mg/mL. (3)

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

- Significant respiratory depression. (4)
- Acute or severe bronchial asthma in an unmonitored setting or in absence of resuscitative equipment. (4)
- Concurrent use of monoamine oxidase inhibitors (MAOIs) or use of MAOIs within the last 14 days. (7)
- Known or suspected gastrointestinal obstruction, including paralytic ileus. (4)
- Hypersensitivity to meperidine or to any other ingredients of the product. (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 DEMEROL 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 DEMEROL 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 DEMEROL Injection in patients with impaired consciousness or coma. (5.12)

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

Most common adverse reactions were lightheadedness, dizziness, sedation, nausea, vomiting and sweating. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer, Inc. at 1-800-438-1985, 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 DEMEROL Injection because they may reduce analgesic effect of DEMEROL Injection or precipitate withdrawal symptoms. (7)

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

- 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)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 12/2025

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 DEMEROL

Addiction, Abuse, and Misuse

Because the use of DEMEROL 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 DEMEROL Injection, especially during initiation or following a dosage increase. To reduce the risk of respiratory depression, proper dosing and titration of DEMEROL Injection 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 DEMEROL 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 DEMEROL 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. Monitor patients receiving DEMEROL Injection and any CYP3A4 inhibitor or inducer *[see Warnings and Precautions (5.5), Drug Interactions (7)]*.

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

Concomitant use of DEMEROL Injection with monoamine oxidase (MAO) inhibitors can result in coma, severe respiratory depression, cyanosis, and hypotension. Use of DEMEROL 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

DEMEROL Injection is indicated for preoperative medication, support of anesthesia, and obstetrical analgesia.

DEMEROL 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 Warnings and Precautions (5.1)]*, reserve opioid analgesics, including DEMEROL 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.

Use of DEMEROL Injection for an extended period of time may increase the risk of toxicity (e.g., seizures) from the accumulation of the meperidine metabolite, normeperidine.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

- DEMEROL 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 DEMEROL 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 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 Warnings and Precautions (5.1)]*.
- Respiratory depression can occur at any time during opioid therapy, especially when initiating and following dosage increases with DEMEROL Injection. Consider this risk when selecting an initial dose and when making dose adjustments *[see Warnings and Precautions (5)]*.
- Inspect DEMEROL Injection for particulate matter and discoloration prior to administration. Do not use if color is darker than pale yellow, if it is discolored in any other way, or if it contains a precipitate.

2.2 For Management of Pain

Initial Dosage

Dosage should be adjusted according to the severity of the pain and the response of the patient. While subcutaneous administration is suitable for occasional use, 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.

Adults: Initiate treatment in a dosing range of 50 mg to 150 mg intramuscularly or subcutaneously every 3 to 4 hours as needed for pain, and at the lowest dose necessary to achieve adequate analgesia. Elderly patients should usually be given meperidine at the lower end of the dose range and observed closely.

Children: Initiate treatment in a dosing range of 0.5 mg/lb to 0.8 mg/lb intramuscularly or subcutaneously up to the adult dose, every 3 to 4 hours as necessary, and at the lowest dose necessary to achieve adequate analgesia.

Titration and Maintenance of Therapy

Titrate the dose based upon the individual patient's response to their initial dose of DEMEROL Injection. Individually titrate DEMEROL Injection to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving DEMEROL 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 health and care 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 DEMEROL 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.

Discontinuation of DEMEROL Injection

When a patient who has been taking DEMEROL Injection regularly and may be physically-dependent no longer requires therapy with DEMEROL Injection, taper the dose gradually, by 25% to 50% every 2 to 4 days, while monitoring carefully 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 DEMEROL Injection in patients who may be physically dependent on opioids *[see Warnings and Precautions (5.15), Drug Abuse and Dependence (9.3)]*.

2.3 For Preoperative Medication

Adults: The usual dosage is 50 mg to 100 mg intramuscularly or subcutaneously, 30 to 90 minutes before the beginning of anesthesia. Elderly patients should usually be given meperidine at the lower end of the dose range and observed closely.

Children: The usual dosage is 0.5 mg/lb to 1 mg/lb intramuscularly or subcutaneously up to the adult dose, 30 to 90 minutes before the beginning of anesthesia.

2.4 For Support of Anesthesia

Repeated slow intravenous Injections of fractional doses (e.g., 10 mg/mL) or continuous intravenous infusion of a more dilute solution (e.g., 1 mg/mL) should be used. The dose should be titrated to the needs of the patient and will depend on the premedication and type of anesthesia being employed, the characteristics of the particular patient, and the nature and duration of the operative procedure. Elderly patients should usually be given meperidine at the lower end of the dose range and observed closely.

2.5 For Obstetrical Analgesia

The usual dosage is 50 mg to 100 mg intramuscularly or subcutaneously when pain becomes regular, and may be repeated at 1- to 3-hour intervals.

2.6 Dosage Modifications with Concomitant Phenothiazines

The dose of DEMEROL 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 DEMEROL Injection.

3 DOSAGE FORMS AND STRENGTHS

DEMEROL Injection is a clear, colorless, sterile aqueous solution, available in the following dosage forms and strengths:

- Single-dose Carpuject™ cartridge with Luer Lock for the Carpuject Syringe System, ONLY to be used with Carpuject™ Holder, and available in the following strengths: 25 mg/mL, 50 mg/mL, 75 mg/mL, and 100 mg/mL.
- Multiple-dose vials containing 0.1% metacresol as a preservative, available in the following strength: 1,500 mg/30 mL (50 mg/mL).
- Single-dose NexJect™ Prefilled Syringe with Luer Lock, available in the following strengths: 25 mg/mL and 50 mg/mL.

4 CONTRAINDICATIONS

DEMEROL 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 (5.9)]*
- Concurrent use of monoamine oxidase inhibitors (MAOIs) or use of MAOIs within the last 14 days *[see Warnings and Precautions (5.6), Drug Interactions (7)]*
- Known or suspected gastrointestinal obstruction, including paralytic ileus *[see Warnings and Precautions (5.13)]*
- Hypersensitivity to meperidine (e.g., anaphylaxis) *[see Adverse Reactions (6)]*

5 WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse, and Misuse

DEMEROL Injection contains meperidine, a Schedule II controlled substance. As an opioid, DEMEROL 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 DEMEROL 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)]*.

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing DEMEROL Injection, and monitor all patients receiving DEMEROL 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 DEMEROL Injection but use in such patients

necessitates intensive counseling about the risks and proper use of DEMEROL 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. 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 DEMEROL 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 DEMEROL Injection are essential *[see Dosage and Administration (2.3)]*. Overestimating the DEMEROL 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 (2.2)]*.

5.3 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of DEMEROL 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.

Advise both patients and caregivers about the risks of respiratory depression and sedation when DEMEROL Injection is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the

benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs *[see Drug Interactions (7)]*.

5.4 Neonatal Opioid Withdrawal Syndrome

Use of DEMEROL 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 DEMEROL 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 (5.2)]*, particularly when an inhibitor is added after a stable dose of DEMEROL Injection is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in DEMEROL Injection treated patients may increase meperidine plasma concentrations and prolong opioid adverse reactions. When using DEMEROL Injection with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in DEMEROL Injection treated patients, monitor patients closely at frequent intervals and consider dosage reduction of DEMEROL Injection until stable drug effects are achieved *[see Drug Interactions (7)]*.

Concomitant use of DEMEROL 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 DEMEROL 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 DEMEROL 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 Drug Abuse and 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 biologic 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 (5.15)]*.

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 meperidine 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, trazodone, 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 DEMEROL 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 DEMEROL 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: DEMEROL Injection treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of DEMEROL 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 DEMEROL Injection and when DEMEROL Injection is given concomitantly with other drugs that depress respiration *[see Warnings and Precautions (5.2)]*.

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

DEMEROL 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 DEMEROL Injection. In patients with circulatory shock, DEMEROL Injection may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of DEMEROL 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), DEMEROL Injection may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for worsening of signs of increasing intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with DEMEROL Injection.

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

5.13 Risks of Gastrointestinal Complications

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

The meperidine in DEMEROL 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 of 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 the accumulation of the meperidine metabolite, normeperidine.

Monitor 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 DEMEROL Injection. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or precipitate withdrawal symptoms.

When discontinuing DEMEROL Injection, gradually taper the dosage *[see Dosage and Administration (2.2)]*. Do not rapidly reduce or abruptly discontinue DEMEROL Injection *[see Drug Abuse and Dependence (9.3)]*.

5.16 Risks of Driving and Operating Machinery

DEMEROL 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 DEMEROL 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

DEMEROL 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 Intravenous Use

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

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 with Concomitant Use of Serotonergic Drugs *[see Warnings and Precautions (5.8)]*
- 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 have occurred.

The most frequently observed adverse reactions include lightheadedness, 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:

Nervous System: Mood changes (e.g., euphoria, dysphoria), weakness, headache, agitation, tremor, involuntary muscle movements (e.g., muscle twitches, myoclonus), severe convulsions, seizures, transient hallucinations and disorientation, confusion, delirium, visual disturbances.

Inadvertent injection about a nerve trunk may result in sensory-motor paralysis which is usually, though not always, transitory.

Gastrointestinal: Dry mouth, constipation, biliary tract spasm.

Cardiovascular: Flushing of the face, tachycardia, bradycardia, palpitation, hypotension *[see Warnings and Precautions (5.18)]*, syncope, phlebitis following intravenous injection.

Genitourinary: Urinary retention.

Allergic: Pruritus, urticaria, other skin rashes, wheal and flare over the vein with intravenous injection. Hypersensitivity reactions, anaphylaxis.
Histamine release leading to hypotension and/or tachycardia, flushing, sweating, and pruritus.

Other: Pain at injection site; local tissue irritation and induration following subcutaneous injection, particularly when repeated; antidiuretic effect.

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.

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 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

Table 1 includes clinically significant drug interactions with DEMEROL Injection.

Table 1: Clinically Significant Drug Interactions with DEMEROL 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 DEMEROL 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 DEMEROL 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 DEMEROL Injection and CYP2B6 and CYP3A4 inhibitors, particularly when an inhibitor is added after a stable dose of DEMEROL Injection is achieved *[see Warnings and Precautions (5.5)]*. 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 DEMEROL Injection until stable drug effects are achieved. Monitor patients for respiratory depression and sedation at frequent intervals. If a CYP3A4 or CYP2B6 inhibitor is discontinued, consider increasing the DEMEROL Injection dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal.
Examples:	Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconizole), protease inhibitors (e.g., ritonavir)
CYP3A4 and CYP2B6 Inducers	
Clinical Impact:	The concomitant use of DEMEROL 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 (5.5)]*. 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 DEMEROL Injection dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal. If a CYP3A4 or CYP2B6 inducer is discontinued, consider DEMEROL Injection dosage reduction and monitor for signs of respiratory depression.
Examples:	Rifampin, carbamazepine, phenytoin

Table 1: Clinically Significant Drug Interactions with DEMEROL Injection	
Benzodiazepines and Other Central Nervous System (CNS) Depressants	
Clinical Impact:	Due to 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 patients closely for signs of respiratory depression and sedation.
Examples:	Benzodiazepines and other sedatives/hypnotics, anxiolytics, 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 DEMEROL 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 DEMEROL 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 DEMEROL 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 DEMEROL 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 DEMEROL 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 DEMEROL 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 DEMEROL Injection 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. 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 0.85 and 1.5 times the total human daily dose of 1200 mg *[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 (5.4)]*.

Labor or Delivery

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid overdose reversal agents, such as naloxone or nalmefene, must be available for reversal of opioid-induced respiratory depression in the neonate. DEMEROL 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 DEMEROL 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 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 (0.85 and 1.5 times the total daily dose of 1200 mg/day based on body surface area). The findings cannot be clearly attributed to maternal toxicity.

8.2 Lactation

Risk Summary

Meperidine appears in the milk of nursing mothers receiving the drug. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DEMEROL Injection and any potential adverse effects on the breastfed infant from DEMEROL Injection or from the underlying maternal condition.

Clinical Considerations

Monitor infants exposed to DEMEROL 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 breastfeeding 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 DEMEROL Injection in patients less than 18 years of age have not been established.

The safety and effectiveness of meperidine in pediatric patients has not been established. Literature reports indicate that meperidine has a slower elimination rate in neonates and young infants compared to older children and adults. Neonates and young infants may also be more susceptible to the effects, especially the respiratory depressant effects. If meperidine use is contemplated in neonates or young infants, any potential benefits of the drug need to be weighed against the relative risk of the patient.

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 DEMEROL Injection slowly in geriatric patients and monitor closely for signs of central nervous system and respiratory depression *[see Warnings and Precautions (5.2)]*.

Meperidine is 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 also 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 DEMEROL Injection slowly in patients with hepatic 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 occur in patients with renal impairment. Meperidine should therefore be used with caution in patients with renal impairment. Titrate the dosage of DEMEROL Injection slowly in patients with renal impairment and monitor closely for signs of central nervous system and respiratory depression.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

DEMEROL Injection contains meperidine, a Schedule II controlled substance.

9.2 Abuse

DEMEROL Injection contains meperidine, a substance with 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 a 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 DEMEROL 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 DEMEROL Injection 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 DEMEROL 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 DEMEROL 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 who abuse drugs and people with substance use disorder. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with inadequate pain control.

DEMEROL 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 DEMEROL Injection

Abuse of DEMEROL Injection poses a risk of overdose and death. The risk is increased with concurrent abuse of DEMEROL 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 a 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.

DEMEROL Injection should not be rapidly reduced or abruptly discontinued in a physically-dependent patient *[see Dosage and Administration (2.4)]*. If DEMEROL Injection is rapidly reduced or abruptly discontinued in a physically-dependent patient, a withdrawal syndrome may occur, typically characterized by restlessness, lacrimation, rhinorrhea, 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. In severe overdose, particularly by the intravenous route, apnea, circulatory collapse, cardiac arrest, and death may occur.

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 measures (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.

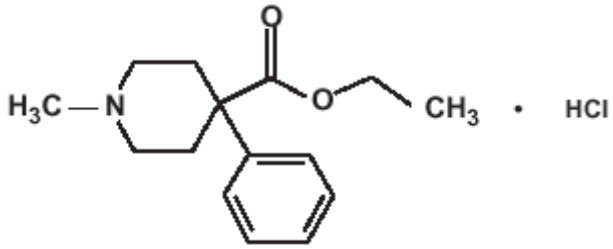
For clinically significant respiratory or circulatory depression secondary to meperidine overdose, administer an opioid overdose reversal agent such as naloxone or nalmefene.

Because the duration of opioid reversal is expected to be less than the duration of action of meperidine in DEMEROL Injection, carefully monitor the patient until spontaneous respiration is reliably re-established. 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 begun with care and by titration with smaller than usual doses of the reversal agent.

11 DESCRIPTION

DEMEROL (meperidine hydrochloride injection) is an opioid agonist available as a sterile aqueous solution, for intramuscular, intravenous, or subcutaneous administration. It contains meperidine hydrochloride as the active pharmaceutical ingredient. Meperidine hydrochloride chemical name is 4-Piperidinecarboxylic acid, 1-methyl-4-phenyl-,ethyl ester, hydrochloride. The molecular weight is 283.79 g/mol. 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, and it is readily soluble in water.

DEMEROL (meperidine hydrochloride injection) is available as:

Single-dose Carpuject™ cartridge with Luer Lock for the Carpuject Syringe System: 25 mg/mL, 50 mg/mL, 75 mg/mL, and 100 mg/mL. Each mL of Single-dose cartridge contains 25 mg, 50 mg, 75 mg or 100 mg of meperidine hydrochloride USP (equivalent to 21.79 mg, 43.58 mg, 65.36 mg or 87.15 mg of meperidine), respectively, and sodium hydroxide NF, and hydrochloric acid NF as pH adjusters, in water for injection. Only the 25 mg strength contains 3.8 mg of sodium chloride USP as isotonicity agent.

Multiple-dose vials: 1,500 mg/30 mL (50 mg/mL) strength. Each mL of vial contains 50 mg of meperidine hydrochloride USP (equivalent to 43.58 mg of meperidine), 1 mg of meta-cresol USP, as a preservative, and sodium hydroxide NF, and hydrochloric acid NF as pH adjusters, in water for injection.

Single-dose NexJect™ Prefilled Syringe with Luer Lock: 25 mg/mL and 50 mg/mL strengths. Each mL contains 25 mg or 50 mg of meperidine hydrochloride USP (equivalent to 21.79 mg or 43.58 mg of meperidine), respectively, and sodium hydroxide NF, and hydrochloric acid NF as pH adjusters, in water for injection. Only the 25 mg strength contains 3.8 mg of sodium chloride USP as isotonicity agent.

The pH of DEMEROL (meperidine hydrochloride injection) solutions is between 3.5 and 6.0.

DEMEROL (meperidine hydrochloride injection) 5 percent solution has a specific gravity of 1.0086 at 20°C, and the 10 percent solution has a specific gravity of 1.0165 at 20°C.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Meperidine hydrochloride is an opioid agonist with multiple actions qualitatively similar to those of morphine; the most prominent of these involve the central nervous system and organs composed of smooth muscle. The principal actions of therapeutic value are analgesia and sedation.

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 pathognomonic (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 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, transient elevations in serum amylase, and opioid-induced esophageal dysfunction (OIED).

Effects of 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, and sweating and/or orthostatic hypotension.

Effects on the Endocrine System

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

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, 2.2)]*.

Meperidine, in 60 mg to 80 mg parenteral doses, is approximately equivalent in analgesic effect to 10 mg of morphine. The onset of action is slightly more rapid than with morphine, and the duration of action is slightly shorter. Meperidine is significantly less effective by the oral than by the parenteral route, but the exact ratio of oral to parenteral effectiveness is unknown.

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, 2.2)]*.

12.3 Pharmacokinetics

Elimination

The half-life of meperidine is 2 to 5 hours, and the half-life of normeperidine is 15 to 30 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.

Specific Population

Hepatic Impairment

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

Age

In clinical studies reported in the literature, changes in several pharmacokinetic parameters with increasing age have been observed. The initial volume of distribution and steady-state volume of distribution 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.

Drug Interactions Studies

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

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

Mutagenesis

Studies in animals to evaluate the mutagenic potential of meperidine have not been conducted.

Impairment of Fertility

Studies to determine the effect of meperidine on fertility have not been conducted.

16 HOW SUPPLIED/STORAGE AND HANDLING

For Parenteral Use

DEMEROL (meperidine hydrochloride injection) is clear and colorless.

DEMEROL (meperidine hydrochloride injection) is supplied as a sterile solution in a multiple-dose vial, single-dose Carpuject™ cartridges for use ONLY with the Carpuject™ Holders and NexJect™ prefilled syringes for subcutaneous, intramuscular, and intravenous administration, and available as follows:

Unit of Sale	**Concentration (per total volume)**
NDC 0409-1181-30 Carton of 1 30 mL fill in 30 mL Multiple-dose Vial	1,500 mg/30 mL (50 mg/mL)
NDC 0409-1176-30 Carton of 10 1 mL fill in 2.5 mL Carpuject™ Single-dose cartridge with Luer Lock	25 mg/mL
NDC 0409-1178-30 Carton of 10	50 mg/mL

Unit of Sale	Concentration (per total volume)
1 mL fill in 2.5 mL Carpuject™ Single-dose cartridge with Luer Lock	
NDC 0409-1179-30 Carton of 10 1 mL fill in 2.5 mL Carpuject™ Single-dose cartridge with Luer Lock	75 mg/mL
NDC 0409-1180-69 Carton of 10 1 mL fill in 2.5 mL Carpuject™ Single-dose cartridge with Luer Lock	100 mg/mL
NDC 0409-1362-01 Clamshell of 10 1 mL fill in 1.5 mL NexJect™ Single-dose Prefilled Syringe with Luer Lock	25 mg/mL
NDC 0409-1418-01 Clamshell of 10 1 mL fill in 1.5 mL NexJect™ Single-dose Prefilled Syringe with Luer Lock	50 mg/mL

Carpuject™ Single-dose cartridges are packaged in a Slim-Pak tamper detection package.

Note that a needle is not included with Carpuject™ Single-dose cartridges and NexJect™ Single-dose Prefilled Syringes.

Carpuject™ and NexJect™ Single-dose products: Discard unused portion.

Multiple-dose vials: Discard unused portion after 28 days.

Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C to 30°C (59°F to 86°F). [See USP Controlled Room Temperature.]

17 PATIENT COUNSELING INFORMATION

Addiction, Abuse, and Misuse

Inform patients that the use of DEMEROL 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)]*. Instruct patients not to share DEMEROL Injection with others and to take steps to protect DEMEROL Injection from theft or misuse.

Life-Threatening Respiratory Depression

Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when DEMEROL 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 (12.1)]*.

Distributed by Hospira, Inc., Lake Forest, IL 60045 USA

Hospira

For Medical Information about DEMEROL Injection, please visit www.pfizermedinfo.com or call 1-800-438-1985.

LAB-0846-13.0

INSTRUCTIONS FOR USE

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if color is darker than pale yellow, if it is discolored in any other way, or if it contains a precipitate.

Instructions for use - Carpuject™ Single-dose Cartridge

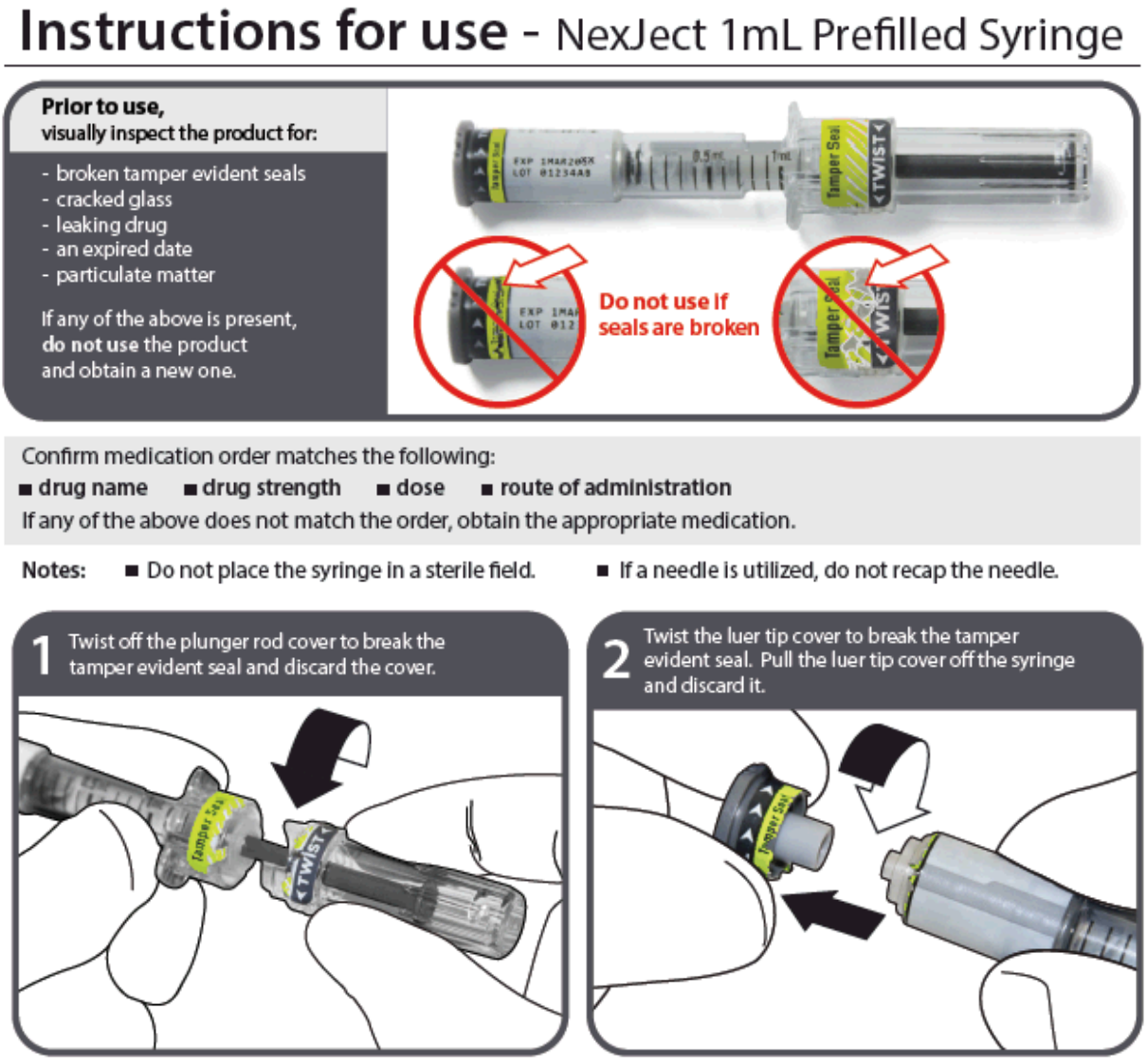
Carpuject™ Single-dose cartridges with Luer Lock are packaged in a Slim-Pak™ tamper detection package. Note that a needle is not included.

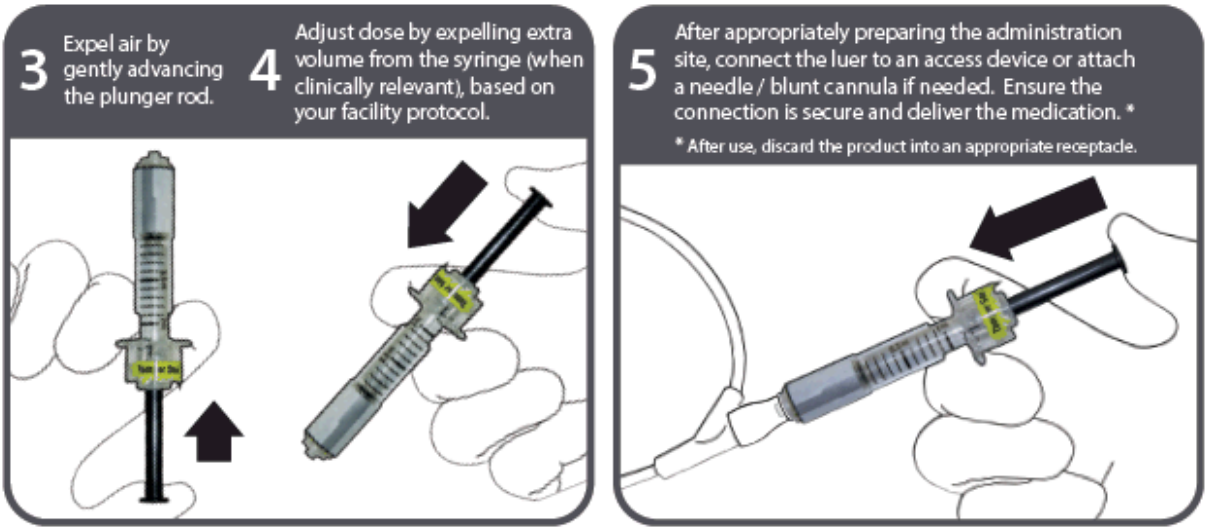
Before use, read all instructions for using the Carpuject™ Syringe, which are contained in the product insert for the reusable Carpuject™ Holder before use.

Carpuject™ Single-dose cartridges are to be used ONLY with Carpuject™ Holders.

NOTE: To prevent needlestick injuries, do not recap, purposely bend, or break by hand used needles. Do not recap, purposely bend, or break by hand blunt Cannulas.

Instructions for use - NexJect™ Single-dose Prefilled Syringe





NOTE: To prevent needlestick injuries, do not recap, purposely bend, or break by hand used needles. Do not recap, purposely bend, or break by hand blunt Cannulas.

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