**HIGHLIGHTS OF PRESCRIBING INFORMATION**

**These highlights do not include all the information needed to use DEMEROL® TABLETS and ORAL SOLUTION safely and effectively. See full prescribing information for DEMEROL TABLETS and ORAL SOLUTION.**

**DEMEROL (meperidine hydrochloride), tablets, for oral use, CII**
**DEMEROL (meperidine hydrochloride), oral solution CII Initial U.S. Approval: 1942**

**WARNING: SERIOUS AND LIFE-THREATENING RISKS FROM USE OF DEMEROL TABLETS AND ORAL SOLUTION**

***See full prescribing information for complete boxed warning.***

- **Ensure accuracy when prescribing, dispensing, and administering DEMEROL Oral Solution. Dosing errors due to confusion between mg and mL, and other Meperidine Hydrochloride Oral Solutions of different concentrations can result in accidental overdose and death. (2.1, 5.1)**
- **DEMEROL Tablets and Oral Solution expose 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. (5.2)**
- **Serious, life-threatening, or fatal respiratory depression may occur, especially upon initiation or following a dosage increase. To reduce the risk of respiratory depression, proper dosing and titration of DEMEROL Tablets or Oral Solution are essential. (5.3)**
- **Accidental ingestion of DEMEROL Tablets or Oral Solution, especially by children, can result in a fatal overdose of meperidine. (5.4)**
- **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. (5.7, 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. (5.5)**
- **Healthcare providers are strongly encouraged to complete a REMS-compliant education program and to counsel patients and caregivers on serious risks, safe use, and the importance of reading the Medication Guide with each prescription. (5.6)**
- **Concomitant use with CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) can result in fatal overdose of meperidine (5.6, 7) Concomitant use of DEMEROL Tablets or Oral Solution with monoamine oxidase inhibitors (MAOIs) can result in coma, severe respiratory depression, cyanosis and hypotension. Use of DEMEROL Tablets or Oral Solution with MAOIs within the last 14 days is contraindicated. (4, 5.8, 6)**

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

| | |
|---|---|
| Boxed Warning | 12/2025 |
| Indications and Usage (1) | 12/2025 |
| Dosage and Administration (2.2, 2.6) | 12/2025 |
| Warnings and Precautions (5.2, 5.3, 5.4, 5.15, 5.16, 5.17) | 12/2025 |

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

DEMEROL Tablets and Oral Solution are opioid agonists indicated 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 Tablets and Oral Solution, 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, 5.2)

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

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

- DEMEROL Tablets and Oral Solution should be prescribed only by healthcare professionals who are knowledgeable about the use of opioids and how to mitigate the associate 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 Tablets and Oral Solution 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 Tablets and Oral Solution. Consider this risk when selecting an initial dose and when making dose adjustments. (2.1, 5.3)
- Discuss opioid overdose reversal agents and options for acquiring them with the patient and/or caregiver, both when initiating and renewing treatment with DEMEROL Tablets and Oral Solution, especially if the patient has additional risk factors for overdose, or close contacts at risk for exposure and overdose. (2.2, 5.2, 5.3, 5.4)
- Adult Patients: Initiate treatment in adults with 50 mg to 150 mg orally, every 3 to 4 hours as needed for pain, and at lowest dose necessary to achieve adequate analgesia (2.3). Titrate the dose based upon the individual patient's response to their initial dose of DEMEROL Tablets and Oral Solution.
- Pediatric Patients: Initiate treatment in pediatric patients with 1.1 mg/kg to 1.8 mg/kg orally, up to the adult dose, every 3 or 4 hours as needed and at the lowest dose necessary to achieve adequate analgesia (2.3). Titrate the dose based upon the individual patient's response to their initial dose of DEMEROL Tablets and Oral Solution.
- Periodically reassess patients receiving DEMEROL Tablets and Oral Solution 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. (2.5)
- Do not rapidly reduce or abruptly discontinue DEMEROL Tablets and Oral Solution in a physically-dependent patient because rapid reduction or abrupt discontinuation of opioid analgesics has resulted in serious withdrawal symptoms, uncontrolled pain, and suicide. (2.5, 5.17)

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

Tablets: 50 mg and 100 mg. (3)
Oral Solution: 50mg/5mL (10 mg/mL)

**----------CONTRAINDICATIONS----------**

- Significant respiratory depression. (4)
- Acute or severe bronchial asthma in an unmonitored setting or in absence of resuscitative equipment. (4)
- Concomitant use of monoamine oxidase inhibitors (MAOIs) or within 14 days of having taken an MAOI. (4)
- 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. (5.9)
- Serotonin Syndrome: Potentially life-threatening condition could result from concomitant serotonergic drug administration. Discontinue DEMEROL Tablets or Oral Solution if serotonin syndrome is suspected. (5.10)
- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Regularly evaluate closely, particularly during initiation and titration. (5.11)
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.12)
- Severe Hypotension: Regularly evaluate during dosage initiation and titration. Avoid use of DEMEROL Tablets or Oral Solution in patients with circulatory shock. (5.13)

- Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness: Regularly evaluate for sedation and respiratory depression. Avoid use of DEMEROL Tablets or Oral Solution in patients with impaired consciousness or coma. (5.14)

**----------ADVERSE REACTIONS----------**

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

**To report SUSPECTED ADVERSE REACTIONS, contact Quagen Pharmaceuticals LLC at 1-888-344-9603 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 Tablets or Oral Solution because they may reduce analgesic effect of DEMEROL Tablets or Oral Solution or precipitate withdrawal symptoms. (7)

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

- Pregnancy: May cause fetal harm (8.1).

**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**

**Rev. 12/2025**

---

**FULL PRESCRIBING INFORMATION: CONTENTS***

**WARNING: SERIOUS AND LIFE-THREATENING RISKS FROM USE OF DEMEROL TABLETS AND ORAL SOLUTION**



* 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 TABLETS AND ORAL SOLUTION**

**Risk of Medication Errors**

**Ensure accuracy when prescribing, dispensing, and administering DEMEROL Oral Solution. Dosing errors due to confusion between mg and mL, and other Meperidine Hydrochloride Oral Solutions of different concentrations can result in accidental overdose and death *[see Dosage and Administration (2.1), Warning and Precautions (5.1)].***

**Addiction, Abuse, and Misuse**

**Because the use of DEMEROL Tablets and Oral Solution 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 (5.2)]*.**

**Life-Threatening Respiratory Depression**

**Serious, life-threatening, or fatal respiratory depression may occur with use of DEMEROL Tablets and Oral Solution, especially during initiation or following a dosage increase. To reduce the risk of respiratory depression, proper dosing and titration of DEMEROL Tablets or Oral Solution are essential *[see Warnings and Precautions (5.3)].***

**Accidental Ingestion**

**Accidental ingestion of DEMEROL Tablets and Oral Solution, especially by children, can result in a fatal overdose of meperidine *[see Warnings and Precautions (5.3)]*.**

**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 Tablets and Oral Solution and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate *[see Warnings and Precautions (5.4), 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 (5.5)]*.**

**Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)**

**Healthcare providers are strongly encouraged to complete a REMS-compliant education program and to counsel patients and caregivers on serious risks, safe use, and the importance of reading the Medication Guide with each prescription *[see Warnings and Precautions (5.6)]*.**

**Cytochrome P450 3A4 (CYP3A4) Interaction**

**The concomitant use of DEMEROL Tablets or Oral Solution with all cytochrome P450 3A4 (CYP3A4) 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 (CYP3A4) inducer may result in an increase in meperidine plasma concentration. Monitor patients receiving DEMEROL Tablets or Oral Solution, and any CYP3A4 inhibitor or inducer *[see Warnings and Precautions (5.7), Drug Interactions (7)]*.**

**Concomitant use of DEMEROL Tablets and Oral Solution with Monoamine Oxidase Inhibitors (MAOIs)**

**Concomitant use of DEMEROL Tablets or Oral Solution with monoamine oxidase inhibitors (MAOIs) can result in coma, severe respiratory depression, cyanosis, and hypotension. Use of DEMEROL Tablets or Oral Solution with MAOIs within last 14 days is contraindicated *[see Contraindications (4), Warnings and Precautions (5.8), Drug Interactions (7)]*.**

## 1 INDICATIONS AND USAGE

DEMEROL Tablets and Oral Solution are indicated for the management of acute 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, reserve opioid analgesics, including DEMEROL Tablets or Oral Solution, 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 Tablet or Oral Solution 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 Oral Solution

Ensure accuracy when prescribing, dispensing, and administering DEMEROL Oral Solution to avoid dosing errors due to confusion between mg and mL, and with other meperidine solutions of different concentrations, which could result in accidental overdose and death. Ensure the proper dose is communicated and dispensed. When writing prescriptions, include both the total dose in mg and the total dose in volume.

Instruct patients and caregivers on how to accurately measure and take or administer the correct dose of DEMEROL Oral Solution.

Strongly advise patients and caregivers to always use a graduated oral syringe or measuring cup, with metric units of measurements (i.e., mL), to correctly measure the prescribed amount of medication.

Inform patients and caregivers that oral dosing devices may be obtained from their pharmacy and to never use household teaspoons or tablespoons to measure DEMEROL Oral Solution.

DEMEROL Tablets and Oral Solution

DEMEROL Tablets and Oral Solution 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 Tablets and Oral Solution 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 to both to the cause of pain and to individual patient factors. Initiate the dosing regimen for each patient individually,

taking into account that 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 Tablets and Oral Solution. Consider this risk when selecting an initial dose and when making dose adjustments *[see Warnings and Precautions (5)]*.

### 2.2 Patient Access to an Opioid Overdose Reversal Agent for the Emergency Treatment of Opioid Overdose

Inform patients and caregivers about opioid overdose reversal agents (e.g., naloxone, nalmefene). Discuss the importance of having access to an opioid overdose reversal agent, especially if the patient has risk factors for overdose (e.g., concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose) or if there are household members (including children) or other close contacts at risk for accidental ingestion or opioid overdose. The presence of risk factors for overdose should not prevent the management of pain in any patient *[see Warnings and Precautions (5.2, 5.3, 5.4)]*.

Discuss the options for obtaining an opioid overdose reversal agent (e.g., prescription, over-the-counter, or as part of a community-based program) *[see Warnings and Precautions (5.3)]*.

There are important differences among the opioid overdose reversal agents, such as route of administration, product strength, approved patient age range, and pharmacokinetics. Be familiar with these differences, as outlined in the approved labeling for those products, prior to recommending or prescribing such an agent.

### 2.3 Initial Dosage

Adults

Initiate treatment with DEMEROL Tablets or Oral Solution in a dosing range of 50 mg to 150 mg orally, every 3 or 4 hours as needed for pain, and at the lowest dose necessary to achieve adequate analgesia. Titrate the dose based upon the individual patient's response to their initial dose of DEMEROL Tablets and Oral Solution.

Pediatric Patients

Initiate treatment with DEMEROL in a dosing range of 1.1 mg/kg to 1.8 mg/kg orally, up to the adult dose, every 3 or 4 hours as needed, and at the lowest dose necessary to achieve adequate analgesia. Titrate the dose based upon the individual patient's response to their initial dose of DEMEROL Tablets and Oral Solution.

### 2.4 Dosage Modification with Concomitant Use with Phenothiazines

The dose of DEMEROL Tablets or Oral Solution should be reduced by 25 to 50% when administered concomitantly with phenothiazines and other tranquilizers.

### 2.5 Titration and Maintenance of Therapy

Individually titrate DEMEROL Tablets and Oral Solution to a dose that provides adequate analgesia and minimizes adverse reactions. If adequate pain management cannot be achieved with a total daily dosage of 600 mg or less, discontinue treatment with DEMEROL Tablets or Oral Solution by tapering the dose and select an alternate analgesic.

Continually reevaluate patients receiving DEMEROL Tablets or Oral Solution 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 (5.2)]*. 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 DEMEROL Tablets or Oral Solution 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.

### 2.6 Safe Reduction or Discontinuation of DEMEROL Tablets and Oral Solution

Do not rapidly reduce or abruptly discontinue DEMEROL Tablets and Oral Solution in patients who may be physically dependent on opioids. Rapid reduction or abrupt discontinuation of opioid analgesics in patients who are physically dependent on opioids has resulted in serious withdrawal symptoms, uncontrolled pain, and suicide. Rapid reduction or abrupt discontinuation has also been associated with attempts to find other sources of opioid analgesics, which may be confused with drug-seeking for abuse. Patients may also attempt to treat their pain or withdrawal symptoms with illicit opioids, such as heroin, and other substances.

When a decision has been made to decrease the dose or discontinue therapy in an opioid-dependent patient taking DEMEROL Tablets and Oral Solution, there are a variety of factors that should be considered, including the total daily dose of opioid (including DEMEROL Tablets and Oral Solution) the patient has been taking, the duration of treatment, the type of pain being treated, and the physical and psychological attributes of the patient. It is important to ensure ongoing care of the patient and to agree on an appropriate tapering schedule and follow- up plan so that patient and provider goals and expectations are clear and realistic. When opioid analgesics are being discontinued due to a suspected substance use disorder, evaluate and treat the patient, or refer for evaluation and treatment of the substance use disorder.

Treatment should include evidence-based approaches, such as medication assisted treatment of opioid use disorder. Complex patients with co-morbid pain and substance use disorders may benefit from referral to a specialist.

There are no standard opioid tapering schedules that are suitable for all patients. Good clinical practice dictates a patient-specific plan to taper the dose of the opioid gradually. For patients on DEMEROL Tablets and Oral Solution who are physically opioid-dependent, initiate the taper by a small enough increment (e.g., no greater than 10% to 25% of the total daily dose) to avoid withdrawal symptoms, and proceed with dose-lowering at an interval of every 2 to 4 weeks. Patients who have been taking opioids for briefer periods of time may tolerate a more rapid taper.

It may be necessary to provide the patient with lower dosage strengths to accomplish a successful taper. Reassess the patient frequently to manage pain and withdrawal symptoms, should they emerge. Common withdrawal symptoms include 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. If withdrawal symptoms arise, it may be necessary to pause the taper for a period of time or raise the dose of the opioid analgesic to the previous dose, and then proceed with a slower taper. In addition, evaluate patients for any changes in mood, emergence of suicidal thoughts, or use of other substances.

When managing patients taking opioid analgesics, particularly those who have been treated for an extended period of time, and/or with high doses for chronic pain, ensure that a multimodal approach to pain management, including mental health support (if needed), is in place prior to initiating an opioid analgesic taper. A multimodal approach to pain management may optimize the treatment of chronic pain, as well as assist with the successful tapering of the opioid analgesic *[see Warnings and Precautions (5.16), Drug Abuse and Dependence (9.3)]*.

## 3 DOSAGE FORMS AND STRENGTHS

Tablets

- 50 mg scored tablet (white, round, convex scored tablets debossed with “T” above “48” on one side and plain on the other side)
- 100 mg scored tablet (white, round, convex tablets debossed with “T” above “49” on one side and plain on the other side)

Oral Solution

- Nonalcoholic, banana-flavored 50 mg per 5 mL (10 mg/mL), bottles of 16 fl. oz.

## 4 CONTRAINDICATIONS

DEMEROL Tablets and Oral Solution are contraindicated in patients with:

- Significant respiratory depression *[see Warnings and Precautions (5.3)]*
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment *[see Warnings and Precautions (5.9)]*
- Concomitant use of monoamine oxidase inhibitors (MAOIs) or within 14 days of having taken an MAOI *[see Drug Interactions (7)]*
- Known or suspected gastrointestinal obstruction, including paralytic ileus *[see Warnings and Precautions (5.15)]*
- Hypersensitivity to meperidine or to any of other ingredients of the product (e.g., anaphylaxis) *[see Adverse Reactions (6)]*

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Risks of Accidental Overdose and Death Due to Medication Errors

Dosing errors can result in accidental overdose and death. Avoid dosing errors that may result from confusion between mg and mL and confusion with meperidine solutions of different concentrations, when prescribing, dispensing, and administering DEMEROL Oral Solution. Ensure that the dose is communicated clearly and dispensed accurately.

Instruct patients and caregivers on how to measure and take or administer the correct dose of DEMEROL Oral Solution and to use extreme caution when measuring the dose. Strongly advise patients to obtain and always use a graduated device that can measure and deliver the prescribed dose accurately, and to never use household teaspoons or tablespoons to measure a dose because these are not accurate measuring devices *[see Dosage and Administration (2.1)]*.

### 5.2 Addiction, Abuse, and Misuse

DEMEROL Tablets and Oral Solution contain meperidine, a Schedule II controlled substance. As an opioid, DEMEROL Tablets and Oral Solution expose 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 Tablets or Oral Solution. Addiction can occur at recommended doses 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 the 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 DEMEROL Tablets and Oral Solution, and reassess all patients receiving DEMEROL Tablets or Oral Solution 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 Tablets and Oral Solution, but use in such patients necessitates intensive counseling about the risks and proper use of DEMEROL Tablets and Oral Solution along with frequent reevaluation for signs of addiction, abuse, and misuse. Consider prescribing an opioid overdose reversal agent *[see Dosage and Administration (2.2), Warnings and Precautions (5.4)]*.

Opioids are sought for nonmedical use and are subject to diversion from legitimate prescribed use. Consider these risks when prescribing or dispensing DEMEROL Tablets and Oral Solution. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on careful storage of the drug during the course of treatment and proper disposal of unused drug 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.

DEMEROL Tablets have been reported as being abused by crushing, chewing, snorting, or injecting the dissolved product. These practices will result in the uncontrolled delivery of the opioid and pose a significant risk to the abuser that could result in overdose or death.

### 5.3 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, 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 Tablets or Oral Solution, the risk is greatest during the initiation of therapy or following a dosage increase of DEMEROL Tablets or Oral Solution.

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

Accidental ingestion of DEMEROL Tablets or Oral Solution, especially by children, can result in respiratory depression and death due to an overdose of meperidine.

Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose.

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 (2.6)]*.

Patient Access to an Opioid Overdose Reversal Agent for the Emergency Treatment of Opioid Overdose

Inform patients and caregivers about opioid overdose reversal agents (e.g., naloxone, nalmefene). Discuss the importance of having access to an opioid overdose reversal agent, especially if the patient has risk factors for overdose (e.g., concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose) or if there are household members (including children) or other close contacts at risk for accidental ingestion or opioid overdose. The presence of risk factors for overdose should not prevent the management of pain in any patient *[see Warnings and Precautions (5.2, 5.4)]*.

Discuss the options for obtaining an opioid overdose reversal agent (e.g., prescription, over-the-counter, or as part of a community-based program).

There are important differences among the opioid overdose reversal agents, such as route of administration, product strength, approved patient age range, and pharmacokinetics. Be familiar with these differences, as outlined in the approved labeling for those products, prior to recommending or prescribing such an agent.

Educate patients and caregivers on how to recognize respiratory depression, and how to use an opioid overdose reversal agent for the emergency treatment of opioid overdose. Emphasize the importance of calling 911 or getting emergency medical help, even if an opioid overdose reversal agent is administered *[see Dosage and Administration (2.2), Warnings and Precautions (5.2, 5.4), Overdosage (10)]*.

### 5.4 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 Tablets or Oral Solution with benzodiazepines and/or other CNS depressants, including alcohol (e.g., non-benzodiazepine sedative/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. Inform patients and caregivers of this potential interaction and educate them on the signs and symptoms of respiratory depression (including sedation).

If concomitant use is warranted, consider recommending or prescribing an opioid overdose reversal agent *[see Dosage and Administration (2.2), Warnings and Precautions (5.3), Overdosage (10)]*.

Advise both patients and caregivers about the risks of respiratory depression and sedation when DEMEROL Tablets or Oral Solution 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)]*.

### 5.5 Neonatal Opioid Withdrawal Syndrome

Use of DEMEROL Tablets and Oral Solution 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 appropriate treatment will be available *[see Use in Specific Populations (8.1)]*.

### 5.6 Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain.
- Discuss the safe use, serious risks, and proper storage and disposal of opioid analgesics with patients and/or their caregivers every time these medications are prescribed. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG.
- Emphasize to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an opioid analgesic is dispensed to them.
- Consider using other tools to improve patient, household, and community safety, such as patient-prescriber agreements that reinforce patient-prescriber responsibilities.

To obtain further information on the opioid analgesic REMS and for a list of accredited REMS CME/CE, call 1-800-503-0784, or log on to www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

### 5.7 Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 (CYP3A4) Inhibitors and Inducers

Concomitant use of DEMEROL Tablets or Oral Solution 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, particularly when an inhibitor is added after a stable dose of DEMEROL Tablets or Oral Solution is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in DEMEROL Tablets or Oral Solution-treated patients may increase meperidine plasma concentrations and prolong opioid adverse reactions. When using DEMEROL and Oral Solution with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in DEMEROL Tablets and Oral Solution-treated patients, evaluate patients at frequent intervals and consider dosage reduction of DEMEROL Tablets and Oral Solution until stable drug effects are achieved.

Concomitant use of DEMEROL Tablets or Oral Solution 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 Tablets and Oral Solution with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, evaluate 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)]*.

### 5.8 Fatal Interaction with Monoamine Oxidase Inhibitors (MAOIs)

Meperidine is contraindicated in patients who are receiving monoamine oxidase inhibitors (MAOIs) 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 pre-existing 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 Tablets or and Oral Solution in patients taking MAOIs or within 14 days of stopping such treatment.

Intravenous hydrocortisone or prednisolone has 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.

### 5.9 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 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 (2.6), Warnings and Precautions (5.17)]*.

### 5.10 Serotonin Syndrome with Concomitant Use of Serotonergic Drugs

Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of DEMEROL Tablets and Oral Solution with serotonergic drugs. Serotonergic drugs include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), St John's wort, 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 MAOIs, 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 Tablets and Oral Solution if serotonin syndrome is suspected.

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

The use of DEMEROL Tablets or Oral Solution 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 Tablets or Oral Solution-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 dosages of DEMEROL Tablets or Oral Solution *[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)]*.

Regularly evaluate patients, particularly when initiating and titrating DEMEROL Tablets and Oral Solution and when DEMEROL Tablets and Oral Solution are given concomitantly with other drugs that depress respiration *[see Warnings and Precautions (5.3), Drug Interactions (7)]*. Alternatively, consider the use of non-opioid analgesics in these patients.

### 5.12 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.

### 5.13 Severe Hypotension

DEMEROL Tablets and Oral Solution 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)]*. Regularly evaluate these patients for signs of hypotension after initiating or titrating the dosage of DEMEROL Tablets or Oral Solution. In patients with circulatory shock, DEMEROL Tablets and Oral Solution may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of DEMEROL Tablets or Oral Solution in patients with circulatory shock.

### 5.14 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 Tablets and Oral Solution 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 DEMEROL Tablets or Oral Solution.

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

### 5.15 Risks of Gastrointestinal Complications

DEMEROL Tablets and Oral Solution are contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.

The meperidine in DEMEROL Tablets and Oral Solution may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Regularly evaluate patients with biliary tract disease, including 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.

### 5.16 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.

Frequently evaluate 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.

### 5.17 Withdrawal

Do not rapidly reduce or abruptly discontinue DEMEROL Tablets or Oral Solution in a patient physically dependent on opioids. When discontinuing DEMEROL Tablets or Oral Solution in a physically dependent patient, gradually taper the dosage. Rapid tapering of meperidine in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain *[see Dosage and Administration (2.6), Drug Abuse and Dependence (9)]*.

Additionally, 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 Tablets and Oral Solution. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or precipitate withdrawal symptoms *[see Drug Interactions (7)]*.

### 5.18 Risks of Driving and Operating Machinery

DEMEROL Tablets and Oral Solution 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 Tablets or Oral Solution and know how they will react to the medication.

### 5.19 Risks in Patients with Pheochromocytoma

In patients with pheochromocytoma, DEMEROL Tablets and Oral Solution has been reported to provoke hypertension.

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

Meperidine 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.

## 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 (5.2)]*
- Life-Threatening Respiratory Depression *[see Warnings and Precautions (5.3)]*
- Interactions with Benzodiazepines or Other CNS Depressants *[see Warnings and Precautions (5.4)]*
- Neonatal Opioid Withdrawal Syndrome *[see Warnings and Precautions (5.5)]*
- Opioid-Induced Hyperalgesia and Allodynia *[see Warnings and Precautions (5.9)]*
- Serotonin Syndrome *[see Warnings and Precautions (5.10)]*
- Adrenal Insufficiency *[see Warnings and Precautions (5.12)]*
- Severe Hypotension *[see Warnings and Precautions (5.13)]*
- Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.15)]*
- Seizures *[see Warnings and Precautions (5.16)]*
- Withdrawal *[see Warnings and Precautions (5.17)]*

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 included 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.

Gastrointestinal: Dry mouth, constipation, biliary tract spasm.

Cardiovascular: Flushing of the face, tachycardia, bradycardia, palpitation, hypotension *[see Warnings and Precautions (5.7)]*, syncope.

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.

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 (5.9)]*.

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 (5.15)]*.

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 Tablets and Oral Solution.

**Table 1: Clinically Significant Drug Interactions with DEMEROL Tablets and Oral Solution**

| **Monoamine Oxidase Inhibitors (MAOIs)** | |
|---|---|
| *Clinical Impact:* | Meperidine is contraindicated in patients who are receiving monoamine oxidase (MAOIs) or those who have recently received such agents.<br>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. |
| *Intervention:* | Do not use DEMEROL Tablets or Oral Solution in patients taking MAOIs or within 14 days of stopping such treatment.<br>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.) |
| *Examples:* | phenelzine, tranylcypromine, linezolid |
| **Inhibitors of CYP3A4 and CYP2B6** | |
| *Clinical Impact:* | The concomitant use of DEMEROL Tablets or Oral Solution 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 Tablets or Oral Solution and CYP2B6 and CYP3A4 inhibitors, particularly when an inhibitor is added after a stable dose of DEMEROL Tablets or Oral Solution is achieved *[see Warnings and Precautions (5.6)]*.<br>After stopping a CYP3A4 or CYP2B6 inhibitor, as the effects of the inhibitor decline, the meperidine plasma concentration will decrease *[see Clinical Pharmacology (12.3)]*, 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 Tablets and Oral Solution until stable drug effects are achieved. Evaluate patients at frequent intervals for respiratory depression and sedation.<br><br>If a CYP3A4 or CYP2B6 inhibitor is discontinued, consider increasing the DEMEROL Tablets and Oral Solution 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 DEMEROL Tablets or Oral Solution and CYP3A4 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 (5.6)]*. 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 Tablets and Oral Solution dosage until stable drug effects are achieved. Assess for signs of opioid withdrawal.<br><br>If a CYP3A4 or CYP2B6 inducer is discontinued, consider DEMEROL Tablets and Oral Solution dosage reduction and evaluate patients at frequent intervals for signs of respiratory depression and sedation. |
| *Examples:* | Rifampin, carbamazepine, phenytoin |
| **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. |
| *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. Inform patients and caregivers of this potential interaction and educate them on the signs and symptoms of respiratory depression (including sedation). If concomitant use is warranted, consider recommending or prescribing an opioid overdose reversal agent *[see Dosage and Administration (2.2), Warnings and Precautions (5.2, 5.4, 5.7)]*. |
| *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 5.10]*. |
| *Intervention:* | If concomitant use is warranted, frequently evaluate the patient, particularly during treatment initiation and dose adjustment. Discontinue DEMEROL Tablets and Oral Solution 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 effect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (i.e., cyclobenzaprine, metaxalone), monoamine oxidase inhibitors (MAOIs) (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 Tablets or Oral Solution 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:* | Because respiratory depression may be greater than otherwise expected, decrease the dosage of DEMEROL Tablets and Oral Solution and/or the muscle relaxant as necessary. Due to the risk of respiratory depression with concomitant use of skeletal muscle relaxants and opioids, consider recommending or prescribing an opioid overdose reversal agent *[see Dosage and Administration (2.2), Warnings and Precautions (5.4, 5.7)]*. |
| *Examples:* | cyclobenzaprine, metaxalone |
| **Diuretics** | |
| *Clinical Impact:* | Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone. |
| *Intervention:* | Evaluate 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:* | Evaluate patients for signs of urinary retention or reduced gastric motility when DEMEROL Tablets and Oral Solution 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 Tablets and Oral Solution is necessary, evaluate 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 of cimetidine and DEMEROL Tablets and Oral Solution is necessary, evaluate 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 (5.5)]*. Available data with DEMEROL Tablets or Oral Solution are insufficient to inform a drug-associated risk for major birth defects and miscarriage or adverse

maternal outcomes. 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 (5.5)]*.

*Labor or Delivery*

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. Resuscitation may be required *[see Overdose (10)]*. An opioid overdose reversal agent, such as naloxone or nalmefene, must be available for reversal of opioid-induced respiratory depression in the neonate. DEMEROL Tablets and Oral Solution are not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate. Opioid analgesics, including DEMEROL Tablets or Oral Solution, 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 Tablets or Oral Solution and any potential adverse effects on the breastfed infant from DEMEROL Tablets or Oral Solution or from the underlying maternal condition.

Clinical Considerations

Monitor infants exposed to DEMEROL Tablets or Oral Solution 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 Toxicology (13.1)].*

### 8.4 Pediatric Use

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

Clinical studies of DEMEROL Tablets and Oral Solution during product development did not include sufficient numbers of subjects aged 65 and over to evaluate age-related differences in safety or efficacy.

Literature reports indicate that geriatric patients have a slower elimination rate compared to young patients and they may be more susceptible to the effects of meperidine. Reducing the total daily dose of meperidine is recommended in elderly patients, and the potential benefits of the drug should be weighed against the relative risk to a geriatric patient.

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 slowly in geriatric patients and frequent reevaluate the patient for signs of central nervous system and respiratory depression *[see Warnings and Precautions (5.11)]*.

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 regularly evaluate 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 DEMEROL Tablets or Oral Solution slowly in patients with hepatic impairment and regularly evaluate 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 DEMEROL Tablets or Oral Solution slowly in patients with renal impairment and regularly evaluate for signs of central nervous system and respiratory depression.

## 9 DRUG ABUSE AND DEPENDENCE

### 9.1 Controlled Substance

DEMEROL Tablets and Oral Solution contain meperidine, a Schedule II controlled substance.

### 9.2 Abuse

DEMEROL Tablets and Oral Solution contain 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 (5.2)]*.

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 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 Tablets and Oral Solution increases risk of overdosage, which may lead to central nervous system and respiratory depression, hypotension, seizures, and death. The risk is increased with concurrent abuse of DEMEROL Tablets and Oral Solution with alcohol and/or other CNS depressants. Abuse of an 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 Tablets and Oral Solution 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 Tablets and Oral Solution 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 Tablets and Oral Solution, like other opioids, can be diverted for non-medical 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 re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Risks Specific to Abuse of DEMEROL Tablets and Oral Solution

Abuse of DEMEROL Tablets and Oral Solution poses a risk of overdose and death. The risk is increased with concurrent use of DEMEROL Tablets and Oral Solution with alcohol and/or other CNS depressants.

DEMEROL Tablets and Oral Solution is approved for oral use only.

DEMEROL Tablets have been reported as being abused by crushing, chewing, snorting, or injecting the dissolved product. Inappropriate intravenous, intramuscular, or subcutaneous use of DEMEROL Tablets or Oral Solution can result in death, local tissue necrosis, infection, pulmonary granulomas, increased risk of endocarditis, and valvular heart injury, and embolism.

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 product 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.

Do not rapidly reduce or abruptly discontinue DEMEROL Tablets and Oral Solution in a patient physically dependent on opioids. Rapid tapering of DEMEROL Tablets and Oral Solution in a patient physically dependent on opioids may lead to serious withdrawal symptoms, uncontrolled pain, and suicide. Rapid discontinuation has also been associated with attempts to find other sources of opioid analgesics, which may be confused with drug-seeking for abuse.

When discontinuing DEMEROL Tablets and Oral Solution, gradually taper the dosage using a patient- specific plan that considers the following: the dose of DEMEROL Tablets and Oral Solution the patient has been taking, the duration of treatment, and the physical and psychological attributes of the patient. To improve the likelihood of a successful taper and minimize withdrawal symptoms, it is important that the opioid tapering schedule is agreed upon by the patient. In patients taking opioids for an extended period of time at high doses, ensure that a multimodal approach to pain management, including mental health support (if needed), is in place prior to initiating an opioid analgesic taper *[see Dosage and Administration (2.6), Warnings and Precautions (5.17)]*.

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 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 opioid overdose, administer an opioid overdose reversal agent such as naloxone or nalmefene.

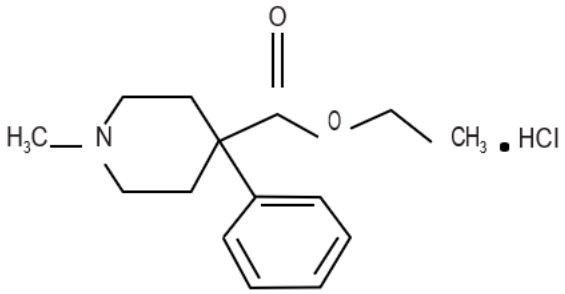
Because the duration of opioid reversal is expected to be less than the duration of action of meperidine in DEMEROL Tablets and Oral Solution, carefully monitor the patient until spontaneous respiration is reliably reestablished. If the response to an opioid overdose reversal agent is suboptimal or only 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 the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of 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.

## 11 DESCRIPTION

DEMEROL (meperidine hydrochloride, USP) Tablet and Oral Solution are opioid agonists. DEMEROL Tablets are available as 50 mg and 100 mg Tablets for oral administration. The chemical name 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.

The Tablets contain 50 mg or 100 mg of meperidine hydrochloride.

The inactive ingredients in DEMEROL Tablets include: calcium sulfate, dibasic calcium phosphate, starch, stearic acid, and talc.

The Oral Solution contains 50 mg of meperidine hydrochloride, per 5 mL (10 mg/mL).

The inactive ingredients in DEMEROL Oral Solution include: benzoic acid, flavor, liquid glucose, purified water, saccharin sodium.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Meperidine 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 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, 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 luteinizing hormone (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 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)]*.

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)]*.

### 12.3 Pharmacokinetics

Absorption

Oral bioavailability of meperidine is approximately 50%.

Elimination

The elimination half-life is 3 to 8 hours in healthy volunteers. The only bioactive metabolite 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 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.

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.

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 to 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

DEMEROL (Meperidine Hydrochloride USP) Tablets, 50 mg (C-II) are white, round, convex scored tablets debossed with “T” above “48” on one side and plain on the other side, and are supplied as: HDPE plastic bottles of 100 (NDC Number 70752-215-10)

DEMEROL (Meperidine Hydrochloride USP) Tablets, 100 mg (C-II) are white, round, convex Tablets debossed with “T” above “49” on one side and plain on the other side, and are supplied as: HDPE plastic bottles of 100 (NDC Number 70752-216-10)

DEMEROL (Meperidine Hydrochloride USP) Oral Solution, 50mg per 5mL (10 mg/mL) (C-II) is non-alcoholic, banana- flavored syrup, and is supplied in 473 mL 16 fl. oz. bottles (NDC Number 70752-217-12).

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

Store DEMEROL Tablets and Oral Solution securely and dispose of properly.

## 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Storage and Disposal

Because of the risks associated with accidental ingestion, misuse, and abuse, advise patients to store DEMEROL Tablets and Oral Solution securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home. Inform patients that leaving DEMEROL Tablets and Oral Solution unsecured can pose a deadly risk to others in the home *[see Warnings and Precautions (5.1, 5.2), Drug Abuse and Dependence (9)]*.

Advise patients and caregivers that when medicines are no longer needed, they should be disposed of promptly. Expired, unwanted, or unused DEMEROL Tablets and Oral Solution should be disposed of by flushing the unused medication down the toilet if a drug take-back option is not readily available. Inform patients that they can visit www.fda.gov/drugdisposal for a complete list of medicines recommended for disposal by flushing, as well as additional information on disposal of unused medicines

Medication Errors

Strongly advise patients and caregivers to always use a graduated oral syringe or measuring cup, with metric units of measurements (i.e., mL), to correctly measure the prescribed amount of medication.

Inform patients and caregivers that oral dosing devices may be obtained from their pharmacy and to never use household teaspoons or tablespoons to measure DEMEROL Oral Solution *[see Warnings and Precautions (5.1)]*.

If the prescribed dosage is changed, instruct patients and caregivers on how to correctly measure the new dose to avoid errors which could result in accidental overdose and death.

Addiction, Abuse, and Misuse

Inform patients that the use of DEMEROL Tablets or Oral Solution, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose and death *[see Warnings and Precautions (5.2)]*. Instruct patients not to share DEMEROL Tablets or Oral Solution with others and to take steps to protect DEMEROL Tablets or Oral Solution 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 starting DEMEROL Tablets or Oral Solution or when the dosage is increased, and that it can occur even at recommended dosages.

Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose *[see Warnings and Precautions (5.4)]*.

Accidental Ingestion

Inform patients that accidental ingestion, especially by children, may result in respiratory depression or death *[see Warnings and Precautions (5.4)]*.

Interactions with Benzodiazepines and Other CNS Depressants

Inform patients and caregivers that potentially fatal additive effects may occur if DEMEROL Tablets or Oral Solution are used with benzodiazepines or other CNS depressants, including alcohol (e.g., non-benzodiazepine sedative/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, gabapentinoids [gabapentin or pregabalin], and other opioids), and not to use these concomitantly unless

supervised by a healthcare provider *[see Warnings and Precautions (5.7), Drug Interactions (7)]*.

Patient Access to an Opioid Overdose Reversal Agent for the Emergency Treatment of Opioid Overdose

Inform patients and caregivers about opioid overdose reversal agents (e.g., naloxone, nalmefene). Discuss the importance of having access to an opioid overdose reversal agent, especially if the patient has risk factors for overdose (e.g., concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose) or if there are household members (including children) or other close contacts at risk for accidental ingestion or opioid overdose.

Discuss with the patient the options for obtaining an opioid overdose reversal agent (e.g., prescription, over-the-counter, or as part of a community-based program) *[see Dosage and Administration (2.2), Warning and Precautions (5.4)]*.

Educate patients and caregivers on how to recognize the signs and symptoms of an overdose.

Explain to patients and caregivers that effects of opioid overdose reversal agents like naloxone and nalmefene are temporary, and that they must call 911 or get emergency medical help right away in all cases of known or suspected opioid overdose, even if an opioid overdose reversal agent is administered *[see Overdosage (10)]*.

Advise patients and caregivers:

- how to treat with the overdose reversal agent in the event of an opioid overdose.
- to tell family and friends about the opioid overdose reversal agent, and to keep it in a place where family and friends can access it in an emergency.
- to read the Patient Information (or other educational material) that will come with their opioid overdose reversal agent. Emphasize the importance of doing this before an opioid emergency happens, so the patient and caregiver will know what to do.

MAOI Interaction

Inform patients not to take DEMEROL Tablets or Oral Solution while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking DEMEROL Tablets or Oral Solution *[see Warnings and Precautions (5.8), Drug Interactions (7)]*.

Hyperalgesia and Allodynia

Inform patients and caregivers not to increase opioid dosage without first consulting a clinician. Advise patients to seek medical attention if they experience symptoms of hyperalgesia, including worsening pain, increased sensitivity to pain, or new pain *[see Warnings and Precautions (5.9); Adverse Reactions (6.2)]*.

Serotonin Syndrome

Inform patients that opioids could cause a rare but potentially life-threatening condition 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. Instruct patients to inform their healthcare providers if they are taking, or plan to take serotonergic medications. *[see Warnings and Precautions (5.10), Drug Interactions (7)]*.

Important Administration Instructions

Instruct patients how to properly take DEMEROL Tablets or Oral Solution *[see Dosage and Administration (2.1), Warnings and Precautions (5.1)]*.

- Strongly advise patients and caregivers to always use a graduated oral syringe/dosing cup when administering DEMEROL Oral Solution to correctly measure the prescribed amount of medication [*see Warnings and Precautions (5.1)]*.
- Instruct patients and caregivers to never use household teaspoons or tablespoons to measure DEMEROL Oral Solution.
- Instruct patients and caregivers not to adjust the dose of DEMEROL Tablets or Oral Solution without

consulting with a physician or other healthcare professional.

- Instruct patients and caregivers to dilute each dose of DEMEROL Oral Solution in one-half glass of water because the undiluted solution may exert a slight topical anesthetic effect on mucous membranes.

Important Discontinuation Instructions

In order to avoid developing withdrawal symptoms, instruct patients not to discontinue DEMEROL Tablets and Oral Solution without first discussing a tapering plan with the prescriber *[see Dosage and Administration (2.6)]*.

Driving or Operating Heavy Machinery

Inform patients that DEMEROL Tablets and Oral Solution may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Advise patients not to perform such tasks until they know how they will react to the medication *[see Warnings and Precautions (5.17)]*.

Constipation

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

Adrenal Insufficiency

Inform patients that opioids could cause adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. Advise patients to seek medical attention if they experience a constellation of these symptoms *[see Warnings and Precautions (5.11)]*.

Hypotension

Inform patients that DEMEROL Tablets or Oral Solution may cause orthostatic hypotension and syncope. Instruct patients how to recognize symptoms of low blood pressure and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position) *[see Warnings and Precautions (5.13)]*.

Anaphylaxis

Inform patients that anaphylaxis has been reported with ingredients contained in DEMEROL Tablets and Oral Solution. Advise patients how to recognize such a reaction and when to seek medical attention *[see Contraindications (4), Adverse Reactions (6)]*.

Pregnancy

*Neonatal Opioid Withdrawal Syndrome*

Inform female patients of reproductive potential that use of DEMEROL Tablets or Oral Solution for an extended period of time during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated *[see Warnings and Precautions (5.5), Use in Specific Populations (8.1)]*.

*Embryo-Fetal Toxicity*

Inform female patients of reproductive potential that DEMEROL Tablets and Oral Solution can cause fetal harm and to inform healthcare provider of a known or suspected pregnancy *[see Use in Specific Populations (8.1)]*.

Lactation

Advise nursing mothers to carefully observe infants for increased sleepiness (more than usual), breathing difficulties, or limpness. Instruct nursing mothers to seek immediate medical care if they notice these signs *[see Use in Specific Populations (8.2)]*.

Infertility

Inform patients that use of opioids for an extended period of time may cause reduced fertility. It is not known

whether these effects on fertility are reversible *[see Use in Specific Populations (8.3)]*.

**Manufactured for and Distributed by:**
Quagen Pharmaceuticals LLC
West Caldwell, NJ 07006

52056

**Medication Guide**
**DEMEROL® (de-meh-rol)**
**(meperidine hydrochloride, USP) Tablets and Oral Solution, CII**

**DEMEROL Tablets and Oral Solution are:**

- A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage the relief short-term (acute) pain, when other pain treatments such as non-opioid pain medicines do not treat your pain well enough or you cannot tolerate them.
- An opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to death.

**Important information about DEMEROL Tablets and Oral Solution:**

- **Get emergency help or call 911 right away if you take too much DEMEROL (overdose)**. When you first start taking DEMEROL Tablets or Oral Solution, when your dose is changed, or if you take too much (overdose), serious or life-threatening breathing problems that can lead to death may occur. Ask your healthcare provider about medicines like naloxone or nalmefene that can be used in an emergency to reverse an opioid overdose.
- Taking DEMEROL Tablets and Oral Solution with other opioid medicines, benzodiazepines, gabapentinoids (gabapentin or pregabalin), alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.
- Never give anyone else your DEMEROL Tablets and Oral Solution. They could die from taking it. Selling or giving away DEMEROL Tablets and Oral Solution is against the law.
- Store DEMEROL Tablets and Oral Solution away from children and in a safe location not accessible by others, including visitors to the home.

**Do not take DEMEROL Tablets and Oral Solution if you have:**

- severe asthma, trouble breathing, or other lung problems.
- a bowel blockage or have narrowing of the stomach or intestines.
- allergy to meperidine

**Before taking DEMEROL Tablets and Oral Solution, tell your healthcare provider if you have a history of:**

- head injury, seizures
- liver, kidney, thyroid problems
- problems urinating
- pancreas or gallbladder problems
- abuse of street or prescription drugs, alcohol addiction, opioid overdose, or mental health problems.

**Tell your healthcare provider if you are:**

- **noticing your pain getting worse.** If your pain gets worse after you take DEMEROL Tablets and Oral Solution, do not take more of DEMEROL Tablets and Oral Solution without first talking to your healthcare provider. Talk to your healthcare provider if the pain you have increases, if you feel more sensitive to pain, or if you have new pain after taking DEMEROL Tablets and Oral Solution.
- **pregnant or planning to become pregnant.** Use of DEMEROL Tablets and Oral Solution for an extended period of time during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- **breastfeeding.** DEMEROL Tablets and Oral Solution passes into breast milk and may harm your baby. Carefully observe infants for increased sleepiness (more than usual), breathing difficulties, or limpness. Seek immediate medical care if you notice these signs.
- living in a household where there are small children or someone who has abused street or prescription drugs
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking DEMEROL Tablets and Oral Solution with certain other medicines can cause serious side effects that could lead to death.

**When taking DEMEROL Tablets and Oral Solution:**

- Do not change your dose. Take DEMEROL Tablets and Oral Solution exactly as prescribed by your healthcare provider. Use the lowest dose possible for the shortest time needed.
- For acute (short-term) pain, you may only need to take DEMEROL Tablets or Oral Solution for a few days. You may have some DEMEROL Tablets or Oral Solution left over that you did not use. See disposal information at the bottom of this section for directions on how to safely throw away (dispose of) your unused DEMEROL Tablets and Oral Solution.

- Always use a graduated measuring device for DEMEROL Oral Solution to correctly measure your dose. Never use a household teaspoon or tablespoon to measure DEMEROL Oral Solution.
- Mix each dose of DEMEROL oral solution into one-half glass of water before swallowing.
- Take your prescribed dose every 3 or 4 hours as needed for pain. Do not take more than your prescribed dose. If you miss a dose, take your next dose at your usual time.
- Call your healthcare provider if the dose you are taking does not control your pain.
- If you have been taking DEMEROL Tablets and Oral Solution regularly, do not stop taking DEMEROL Tablets and Oral Solution without talking to your healthcare provider.
- Dispose of expired, unwanted, or unused DEMEROL Tablets and Oral Solution by promptly flushing down the toilet, if a drug take-back option is not readily available. Visit www.fda.gov/drugdisposal for additional information on disposal of unused medicines.

**While taking DEMEROL Tablets and Oral Solution DO NOT:**

- Drive or operate heavy machinery, until you know how DEMEROL Tablets or Oral Solution affects you. DEMEROL Tablets or Oral Solution can make you sleepy, dizzy, or lightheaded.
- Drink alcohol or use prescription or over-the-counter medicines that contain alcohol. Using products containing alcohol during treatment with DEMEROL Tablets or Oral Solution may cause you to overdose and die.

**The possible side effects of DEMEROL Tablets and Oral Solution:**

- constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain. Call your healthcare provider if you have any of these symptoms and they are severe.

**Get emergency medical help or call 911 right away if you have:**

- trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue, or throat, extreme drowsiness, light-headedness when changing positions, feeling faint, agitation, high body temperature, trouble walking, stiff muscles, or mental changes such as confusion.

These are not all the possible side effects of DEMEROL Tablets and Oral Solution. Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

**For more information go to dailymed.nlm.nih.gov**

**Manufactured and Distributed by:** Quagen Pharmaceuticals LLC, West Caldwell, NJ, 07006
www.quagenpharma.com or call 1-888-344-9603

**This Medication Guide has been approved by the U.S. Food and Drug Administration.** Rev. 12/2025