MEPERIDINE HYDROCHLORIDE TABLETS, USP Rx Only

050

Rev. 03-2017-00

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use MEPERIDINE HYDROCHLORIDE TABLETS safely and effectively. See full prescribing information for MEPERIDINE HYDROCHLORIDE TABLETS.

MEPERIDINE HYDROCHLORIDE tablets, for oral use, CII

Initial U.S. Approval: 1942

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS; and MONOAMINE OXIDASE INHIBITORS (MAOIs) INTERACTIONS

See full prescribing information for complete boxed warning.

- **Meperidine hydrochloride tablets expose users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patient's risk before prescribing and monitor regularly for these behaviors and conditions. (5.1)**
- **Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. (5.2)**
- **Accidental ingestion of meperidine hydrochloride tablets, especially by children, can result in a fatal overdose of meperidine. (5.2)**
- **Prolonged use of meperidine hydrochloride tablets during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.3)**
- **Concomitant use with CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) can result in fatal overdose of meperidine. (5.4, 7)**
- **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; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation. (5.5, 7)**
- **Concomitant use of meperidine hydrochloride tablets with monoamine oxidase inhibitors (MAOIs) can result in coma, severe respiratory depression, cyanosis and hypotension. Use of meperidine hydrochloride tablets with MAOIs within the last 14 days is contraindicated. (4, 5.6, 6)**

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

Boxed Warning	12/2016
Indications and Usage (1)	12/2016
Dosage and Administration (2)	12/2016
Contraindications (4)	12/2016
Warnings and Precautions (5)	12/2016

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

Meperidine is an opioid agonist indicated for the management of pain, severe enough to require an opioid analgesic and for which alternative treatments are inadequate. (1)

Limitations of Use (1)

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, reserve meperidine hydrochloride tablets for use in patients for whom alternative treatment options [e.g., non-opioid analgesics or opioid combination products]:

- Have not been tolerated, or are not expected to be tolerated,
- Have not provided adequate analgesia, or are not expected to provide adequate analgesia.

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

- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals. (2.1)
- Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse. (2.1)
- Adult Patients: Initiate treatment in adults with 50 mg to 150 mg every 3 to 4 hours as needed for pain. (2.2)
- Pediatric Patients: Initiate treatment with 1.1 mg/kg to 1.8 mg/kg orally, up to the adult dose, every 3 or 4 hours as needed for pain. (2.2)
- Do not stop meperidine hydrochloride tablets abruptly in a physically dependent patient. (2.5)

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

Tablets: 50 mg and 100 mg. (3)

-----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-----

- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Monitor closely, particularly during initiation and titration. (5.7)
- Serotonin Syndrome: Potentially life-threatening condition could result from concomitant serotonergic drug administration. Discontinue meperidine hydrochloride tablets if serotonin syndrome is suspected. (5.8)
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.9)
- Severe Hypotension: Monitor during dosage initiation and titration. Avoid use of meperidine hydrochloride tablets in patients with circulatory shock. (5.10)
- Risks of Use in Patients with Increased Intracranial Pressure Brain Tumors, Head Injury, or Impaired Consciousness: Monitor for sedation and respiratory depression. Avoid use of meperidine hydrochloride tablets in patients with impaired consciousness or coma. (5.11)

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

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

To report SUSPECTED ADVERSE REACTIONS, contact Epic Pharma, LLC at 1-888-374-2791 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 meperidine hydrochloride tablets because they may reduce analgesic effect of meperidine hydrochloride tablets 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.

Revised: 3/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS; and MONOAMINE OXIDASE INHIBITORS (MAOIs) INTERACTIONS

Addiction, Abuse, and Misuse

Meperidine hydrochloride tablets 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 meperidine hydrochloride tablets, and monitor all patients regularly for the development of these behaviors and conditions *[see Warnings and Precautions (5.1)]*.

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of meperidine hydrochloride tablets. Monitor for respiratory depression, especially during initiation of meperidine hydrochloride tablets or following a dose increase *[see Warnings and Precautions (5.2)]*.

Accidental Ingestion

Accidental ingestion of meperidine hydrochloride tablets, especially by children, can result in a fatal overdose of meperidine *[see Warnings and Precautions (5.2)]*.

Neonatal Opioid Withdrawal Syndrome

Prolonged use of meperidine hydrochloride tablets during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Warnings and Precautions (5.3)]*.

Cytochrome P450 3A4 (CYP3A4) Interaction

The concomitant use of meperidine hydrochloride tablets 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 meperidine hydrochloride tablets and any CYP3A4 inhibitor or inducer *[see Warnings and Precautions (5.4), Drug Interactions (7)]*.

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 *[see Warnings and Precautions (5.5), Drug Interactions (7)]*.

- **Reserve concomitant prescribing of meperidine hydrochloride tablets and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

Concomitant use of Meperidine Hydrochloride Tablets with Monoamine Oxidase Inhibitors (MAOIs)

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

1 INDICATIONS AND USAGE

Meperidine hydrochloride tablets 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, and misuse with opioids, even at recommended doses *[see Warnings and Precautions (5.1)]*, reserve meperidine hydrochloride tablets for use in patients for whom alternative treatment options [e.g., non-opioid analgesics or opioid combination products]:

- Have not been tolerated, or are not expected to be tolerated,
- Have not provided adequate analgesia, or are not expected to provide adequate analgesia.

Meperidine hydrochloride tablets should not be used for treatment of chronic pain. Prolonged meperidine hydrochloride tablets use 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

Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals *[see Warnings and Precautions (5)]*.

Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse *[see Warnings and Precautions (5.1)]*.

Monitor patients closely for respiratory depression, especially within the first 24 to 72 hours of initiating therapy and following dosage increases with meperidine hydrochloride tablets and adjust the dosage accordingly *[see Warnings and Precautions (5.2)]*.

2.2 Initial Dosage

Adults

Initiate treatment with meperidine hydrochloride tablets in a dosing range of 50 mg to 150 mg orally, every 3 or 4 hours as needed for pain.

Pediatric Patients

Initiate treatment with meperidine hydrochloride tablets 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 necessary.

2.3 Dosage Modification with Concomitant Use with Phenothiazines

The dose of meperidine should be reduced by 25 to 50% when administered concomitantly with phenothiazines and other tranquilizers.

2.4 Titration and Maintenance of Therapy

Individually titrate meperidine hydrochloride tablets 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 meperidine by tapering the dose and select an alternate analgesic.

Continually reevaluate patients receiving meperidine to assess the maintenance of pain control and the relative incidence of adverse reactions, as well as monitoring for the development of addiction, abuse, or misuse *[see Warnings and Precautions (5.1)]*. 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 meperidine hydrochloride tablets dosage. If unacceptable opioid-related adverse reactions are observed, consider reducing the dosage. Adjust the dosage to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

2.5 Discontinuation of Meperidine Hydrochloride Tablets

When a patient who has been taking meperidine hydrochloride tablets regularly and may be physically dependent no longer requires therapy with meperidine hydrochloride tablets, taper the dose gradually, by 25% to 50% every 2 to 4 days, while monitoring carefully for signs and symptoms of withdrawal. If the patient develops these signs or symptoms, raise the dose to the previous level and taper more slowly, either by increasing the interval between decreases, decreasing the amount of change in dose, or both. Do not abruptly discontinue meperidine hydrochloride tablets in a physically-dependent patient. *[see Warnings and Precautions (5.14), Drug Abuse and Dependence (9)]*.

3 DOSAGE FORMS AND STRENGTHS

- 50 mg tablet (white, round biconvex tablets, debossed "∈" above bisect and "50" below bisect on one side, plain on the other side)
- 100 mg tablet (white, round biconvex tablets, debossed "∈51" on one side and bisected on the other side)

4 CONTRAINDICATIONS

Meperidine hydrochloride tablets are contraindicated in patients with:

- Significant respiratory depression *[see Warnings and Precautions (5.2)]*
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment *[see Warnings and Precautions (5.7)]*
- Concomitant use of monoamine oxidase inhibitors (MAOIs) or within 14 days of having taken an MAOI. *[see Drug Interactions (7)]*
- Known or suspected gastrointestinal obstruction, including paralytic ileus *[see Warnings and Precautions (5.12)]*
- 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 Addiction, Abuse, and Misuse

Meperidine hydrochloride tablets contain meperidine, a Schedule II controlled substance. As an opioid, meperidine hydrochloride tablets exposes users to the risks of addiction, abuse and misuse *[see Drug Abuse and Dependence (9)]*.

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed meperidine hydrochloride tablets. Addiction can occur at recommended dosages and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing meperidine hydrochloride tablets, and monitor all patients receiving meperidine hydrochloride tablets 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 meperidine hydrochloride tablets, but use in such patients necessitates intensive counseling about the risks and proper use of meperidine hydrochloride tablets along with intensive monitoring for signs of addiction, abuse, and misuse.

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing meperidine hydrochloride tablets. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug *[see Patient Counseling Information (17)]*. 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.

Meperidine hydrochloride 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.

5.2 Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, 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 meperidine hydrochloride tablets, the risk is greatest during the initiation of therapy or following a dosage increase. Monitor patients closely for respiratory depression, especially within the first 24 to 72 hours of initiating therapy with and following dosage increases of meperidine hydrochloride tablets.

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

Accidental ingestion of meperidine hydrochloride tablets, especially by children, can result in respiratory depression and death due to an overdose of meperidine.

5.3 Neonatal Opioid Withdrawal Syndrome

Prolonged use of meperidine hydrochloride tablets 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 a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Use in Specific Populations (8.1), Patient Counseling Information (17)]*.

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

Concomitant use of meperidine hydrochloride tablets 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 meperidine hydrochloride tablets is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in meperidine hydrochloride tablets-treated patients may increase meperidine plasma concentrations and prolong opioid adverse reactions. When using meperidine with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in meperidine hydrochloride tablets-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of meperidine hydrochloride tablets until stable drug effects are achieved *[see Drug Interactions (7)]*.

Concomitant use of meperidine hydrochloride tablets 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 meperidine hydrochloride tablets with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur *[see Drug Interactions (7)]*.

5.5 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of meperidine hydrochloride tablets with benzodiazepines or other CNS depressants (e.g., nonbenzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). 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. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when meperidine hydrochloride tablets are 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), Patient Counseling Information (17)]*.

5.6 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 preexisting hyperphenylalaninemia. Some have been characterized by coma, severe respiratory depression, cyanosis, and hypotension, and have resembled the syndrome of acute narcotic 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 meperidine hydrochloride tablets in patients taking MAOIs or within 14 days of stopping such treatment.

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

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

The use of meperidine hydrochloride tablets 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: Meperidine hydrochloride tablets-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 meperidine hydrochloride tablets *[see Warnings and Precautions (5.2)]*.

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

Monitor such patients closely, particularly when initiating and titrating meperidine hydrochloride tablets and when meperidine hydrochloride tablets are given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients.

5.8 Serotonin Syndrome with Concomitant Use of Serotonergic Drugs

Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of meperidine hydrochloride tablets 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), 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). The onset of symptoms generally occurs within several hours to a few days of concomitant use, but may occur later than that. Discontinue meperidine hydrochloride tablets if serotonin syndrome is suspected.

5.9 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.

5.10 Severe Hypotension

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

5.11 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), meperidine 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 meperidine hydrochloride tablets.

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

5.12 Risks of Use in Patients with Gastrointestinal Conditions

Meperidine hydrochloride tablets are contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.

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

5.13 Increased Risk of Seizures in Patients with Seizure Disorders

The meperidine in meperidine hydrochloride tablets may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures occurring in other clinical settings associated with seizures. If dosage is escalated substantially above recommended levels because of tolerance development, seizures may occur in individuals without a history of seizures disorders. Monitor patients with a history of seizure disorders for worsened seizure control during meperidine hydrochloride tablets therapy. Prolonged meperidine use may increase the risk of toxicity (e.g., seizures) from the accumulation of the meperidine metabolite, normeperidine.

5.14 Withdrawal

Avoid the use of mixed agonist/antagonist (e.g., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., buprenorphine) analgesics in patients who are receiving a full opioid agonist analgesic, including meperidine hydrochloride tablets. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or precipitate withdrawal symptoms due to competitive blocking of receptors.

When discontinuing meperidine hydrochloride tablets in a physically-dependent patient, gradually taper the dosage *[see Dosage and Administration (2.5)]*. Do not abruptly discontinue meperidine hydrochloride tablets in these patients *[see Drug Abuse and Dependence (9)]*.

5.15 Risks of Driving and Operating Machinery

Meperidine hydrochloride tablets 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 meperidine hydrochloride tablets and know how they will react to the medication *[see Patient Counseling Information (17)]*.

5.16 Risks in Patients with Pheochromocytoma

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

5.17 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 (5.1)]*
- Life-Threatening Respiratory Depression *[see Warnings and Precautions (5.2)]*
- Neonatal Opioid Withdrawal Syndrome *[see Warnings and Precautions (5.3)]*
- Interactions with Benzodiazepines or Other CNS Depressants *[see Warnings and Precautions (5.5)]*
- Serotonin Syndrome *[see Warnings and Precautions (5.8)]*
- Adrenal Insufficiency *[see Warnings and Precautions (5.9)]*
- Severe Hypotension *[see Warnings and Precautions (5.10)]*
- Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.12)]*
- Seizures *[see Warnings and Precautions (5.13)]*
- Withdrawal *[see Warnings and Precautions (5.14)]*

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, 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 (5.6)]*, 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 chronic use of opioids *[see Clinical Pharmacology (12.2)]*.

7 DRUG INTERACTIONS

Table 1 includes clinically significant drug interactions with meperidine hydrochloride tablets.

Table 1: Clinically Significant Drug Interactions with Meperidine Hydrochloride Tablets

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. 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 narcotic 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 meperidine hydrochloride tablets in patients taking MAOIs or within 14 days of stopping such treatment. Intravenous hydrocortisone or prednisolone have been used to treat severe reactions, with the addition of intravenous chlorpromazine in those cases exhibiting hypertension and hyperpyrexia. The usefulness and safety of narcotic antagonists in the treatment of these reactions is unknown.)
Examples:	phenelzine, tranylcypromine, linezolid
Inhibitors of CYP3A4 and CYP2B6	
Clinical Impact:	The concomitant use of meperidine hydrochloride tablets 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 meperidine hydrochloride tablets and CYP2B6 and CYP3A4 inhibitors, particularly when an inhibitor is added after a stable dose of meperidine hydrochloride tablets is achieved *[see Warnings and Precautions (5.4)]*. 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.

Medication Guide
Meperidine Hydrochloride
(me-PER-ih-deen HYE-droe-KLOR-ide)
Tablets USP, CII

Meperidine hydrochloride tablets are:

- A strong prescription pain medicine that contain 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 meperidine hydrochloride tablets:

- **Get emergency help right away if you take too many meperidine hydrochloride tablets (overdose).** When you first start taking meperidine hydrochloride tablets, 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.
- Taking meperidine hydrochloride tablets with other opioid medicines, benzodiazepines, 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 meperidine hydrochloride tablets. They could die from taking it. Store meperidine hydrochloride tablets away from children and in a safe place to prevent stealing or abuse. Selling or giving away meperidine hydrochloride tablets is against the law.

Do not take meperidine hydrochloride tablets 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 meperidine hydrochloride tablets, tell your healthcare provider if you have a history of:

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

Tell your healthcare provider if you are:

- **pregnant or planning to become pregnant.** Prolonged use of meperidine hydrochloride tablets during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- **breastfeeding.** Meperidine passes into breast milk and may harm your baby.
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking meperidine hydrochloride tablets with certain other medicines can cause serious side effects that could lead to death.

When taking meperidine hydrochloride tablets:

- Do not change your dose. Take meperidine hydrochloride tablets exactly as prescribed by your healthcare provider. Use the lowest dose possible for the shortest time needed.
- Take your prescribed dose every 3 or 4 hours as necessary. 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 meperidine hydrochloride tablets regularly, do not stop taking meperidine hydrochloride tablets without talking to your healthcare provider.
- After you stop taking meperidine hydrochloride tablets, flush any unused tablets down the toilet.

While taking meperidine hydrochloride tablets DO NOT:

- Drive or operate heavy machinery, until you know how meperidine hydrochloride tablets affect you. Meperidine 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 meperidine hydrochloride tablets may cause you to overdose and die.

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MEPERIDINE HYDROCHLORIDE TABLETS, USP

Rx Only

The possible side effects of meperidine:

- 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 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 meperidine. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. **For more information go to dailymed.nlm.nih.gov**

Manufactured by: Epic Pharma LLC, Laurelton, NY 11413, call Epic Pharma, LLC at 1-888-374-2791

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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Intervention:	If concomitant use is necessary, consider dosage reduction of meperidine hydrochloride tablets until stable drug effects are achieved. Monitor patients for respiratory depression and sedation at frequent intervals. If a CYP3A4 or CYP2B6 inhibitor is discontinued, consider increasing the meperidine hydrochloride tablets dosage until stable drug effects are achieved. Monitor 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 meperidine hydrochloride tablets 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 (5.4)]*. After stopping a CYP3A4 or CYP2B6 inducer, as the effects of the inducer decline, the meperidine plasma concentration will increase *[see Clinical Pharmacology (12.3)]*, which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression.
Intervention:	If concomitant use is necessary, consider increasing the meperidine hydrochloride tablets dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal. If a CYP3A4 or CYP2B6 inducer is discontinued, consider meperidine hydrochloride tablets dosage reduction and monitor for signs of respiratory depression.
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. Follow patients closely for signs of respiratory depression and sedation *[see Warnings and Precautions (5.5)]*.
Examples:	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol
Serotonergic Drugs	
Clinical Impact:	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome *[see Warnings and Precautions (5.8)]*.
Intervention:	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue meperidine hydrochloride tablets 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), 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 meperidine hydrochloride tablets and/or precipitate withdrawal symptoms.
Intervention:	Avoid concomitant use.
Examples:	butorphanol, nalbuphine, pentazocine, buprenorphine
Muscle Relaxants	
Clinical Impact:	Meperidine may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
Intervention:	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of meperidine hydrochloride tablets and/or the muscle relaxant as necessary.
Diuretics	
Clinical Impact:	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
Intervention:	Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Anticholinergic Drugs	
Clinical Impact:	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Intervention:	Monitor patients for signs of urinary retention or reduced gastric motility when meperidine hydrochloride tablets 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 meperidine hydrochloride tablets is necessary, monitor patients for respiratory depression and sedation at frequent intervals.
Cimetidine	
Clinical Impact:	The concomitant use of cimetidine may reduce the clearance and volume of distribution of meperidine also the formation of the metabolite, normeperidine, in healthy subjects.
Intervention:	If concomitant use of cimetidine and meperidine hydrochloride tablets is necessary, monitor patients for respiratory depression and sedation at frequent intervals.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome *[see Warnings and Precautions (5.3)]*. Available data with meperidine hydrochloride tablets are insufficient to inform a drug-associated risk for major birth defects and miscarriage. 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]*.

Adverse outcomes in pregnancy can occur regardless of the health of the mother or the use of medications. 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

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth.

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

Labor and Delivery

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

Clinical Considerations

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

8.3 Females and Males of Reproductive Potential

Infertility

Chronic use of opioids 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 meperidine hydrochloride tablets 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 meperidine hydrochloride tablets slowly in geriatric patients and monitor closely for signs of central nervous system and respiratory depression *[see Warnings and Precautions (5.5, 5.7)]*.

Meperidine is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

8.6 Hepatic Impairment

Accumulation of meperidine and/or its active metabolite, normeperidine, can 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 meperidine hydrochloride tablets slowly in patients with hepatic impairment and monitor closely for signs of central nervous system and respiratory depression.

8.7 Renal Impairment

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

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Meperidine hydrochloride tablets contain meperidine, a Schedule II controlled substance.

9.2 Abuse

Meperidine hydrochloride tablets contain meperidine, a substance with a high potential for abuse similar to other opioids including fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, and tapentadol. Meperidine hydrochloride tablets can be abused and is subject to misuse, addiction, and criminal diversion *[see Warnings and Precautions (5.1)]*.

All patients treated with opioids require careful monitoring for signs of abuse and addiction, since use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

"Drug seeking" behavior is very common in addicts and drug abusers. 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 drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Healthcare providers should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

Meperidine hydrochloride tablets, 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 Meperidine Hydrochloride Tablets

Meperidine hydrochloride tablets are for oral use only. Abuse of meperidine hydrochloride tablets poses a risk of overdose and death. Meperidine hydrochloride tablets have been reported as being abused by crushing, chewing, snorting, or injecting the dissolved product. The risk is increased with concurrent use of meperidine hydrochloride tablets with alcohol and other central nervous system depressants. In addition, 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 chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dosage reduction of a drug. Withdrawal also 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 opioid usage.

Meperidine hydrochloride tablets should not be abruptly discontinued *[see Dosage and Administration (2.5)]*. If meperidine hydrochloride tablets are abruptly discontinued in a physically-dependent patient, a withdrawal syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia and mydriasis. Other signs and symptoms also may develop, including irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

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

10 OVERDOSAGE

Clinical Presentation

Acute overdose with meperidine hydrochloride tablets 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, 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)]*.

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 techniques.

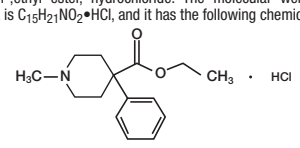
The opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to meperidine overdose, administer an opioid antagonist. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to meperidine overdose.

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

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

11 DESCRIPTION

Meperidine hydrochloride tablet is an opioid agonist, 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 283.79. Its molecular formula is $C_{15}H_{21}NO_2 \bullet HCl$, 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 meperidine hydrochloride tablets include: pregelatinized starch, microcrystalline cellulose, lactose monohydrate, silicon dioxide and stearic acid.

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, and transient elevations in serum amylase.

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.

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

Effects on the Immune System

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

Concentration–Efficacy Relationships

The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. 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 postoperative 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 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

Meperidine Hydrochloride Tablets USP, 50 mg are white, round biconvex tablets, debossed "∈" above bisect and "50" below bisect on one side, plain on the other side, available in bottles of 100.

Meperidine Hydrochloride Tablets USP, 100 mg are white, round biconvex tablets, debossed "∈51" on one side and bisected on the other side, available in bottles of 100.

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

Store at 20° to 25° C (68° to 77° F) [See USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

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

Addiction, Abuse, and Misuse

Inform patients that the use of meperidine hydrochloride tablets, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose and death *[see Warnings and Precautions (5.1)]*. Instruct patients not to share meperidine hydrochloride tablets with others and to take steps to protect meperidine hydrochloride tablets 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 meperidine hydrochloride tablets or when the dosage is increased, and that it can occur even at recommended dosages *[see Warnings and Precautions (5.2)]*. Advise patients how to recognize respiratory depression and to seek medical attention if breathing difficulties develop.

Accidental Ingestion

Inform patients that accidental ingestion, especially by children, may result in respiratory depression or death *[see Warnings and Precautions (5.2)]*. Instruct patients to take steps to store meperidine hydrochloride tablets securely and to flush any unused tablets of meperidine hydrochloride tablets down in the toilet.

Interactions with Benzodiazepines and Other CNS Depressants

Inform patients and caregivers that potentially fatal additive effects may occur if meperidine hydrochloride tablets are used with benzodiazepines or other CNS depressants, including alcohol, and not to use these concomitantly unless supervised by a healthcare provider *[see Warnings and Precautions (5.5), Drug Interactions (7)]*.

MAOI Interaction

Inform patients not to take meperidine hydrochloride tablets while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking meperidine hydrochloride tablets *[see Warnings and Precautions (5.6), Drug Interactions (7)]*.

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 (5.8), Drug Interactions (7)]*.

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 (5.9)]*.

Important Administration Instructions

Instruct patients how to properly take meperidine hydrochloride tablets.

- Advise patients not to adjust the dose of meperidine hydrochloride tablets without consulting with a physician or other healthcare professional.
- If patients have been receiving treatment with meperidine hydrochloride tablets for more than a few weeks and cessation of therapy is indicated, counsel them on the importance of safely tapering the dose as abrupt discontinuation of the medication could precipitate withdrawal symptoms. Provide a dose schedule to accomplish a gradual discontinuation of the medication *[see Dosage and Administration (2.5)]*.

Hypotension

Inform patients that meperidine hydrochloride tablets 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 (5.10)]*.

Anaphylaxis

Inform patients that anaphylaxis has been reported with ingredients contained in meperidine hydrochloride tablets. 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 prolonged use of meperidine hydrochloride tablets during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated *[see Warnings and Precautions (5.3), Use in Specific Populations (8.1)]*.

Embryo-Fetal Toxicity

Inform female patients of reproductive potential that meperidine hydrochloride tablets 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 monitor 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 chronic use of opioids may cause reduced fertility. It is not known whether these effects on fertility are reversible *[see Use in Specific Populations (8.3)]*.

Driving or Operating Heavy Machinery

Inform patients that meperidine hydrochloride tablets 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 (5.15)]*.

Constipation

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

Disposal of Unused MEPERIDINE HYDROCHLORIDE TABLETS

Advise patients to flush any unused tablets down in the toilet.

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