

MEPERIDINE HYDROCHLORIDE- meperidine hydrochloride tablet
MEPERIDINE HYDROCHLORIDE- meperidine hydrochloride solution
West-Ward Pharmaceuticals Corp.

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

MEPERIDINE HYDROCHLORIDE tablets, for oral use CII

MEPERIDINE HYDROCHLORIDE oral solution, CII

Initial U.S. Approval: 1942

WARNING: RISK OF MEDICATION ERRORS; ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); 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.

- **Ensure accuracy when prescribing, dispensing, and administering Meperidine Hydrochloride 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)**
- **Meperidine Hydrochloride 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 monitor regularly for these behaviors and conditions. (5.2)**
- **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. (5.3)**
- **Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. (5.4)**
- **Accidental ingestion of Meperidine Hydrochloride Tablets or Oral Solution, especially by children, can result in a fatal overdose of meperidine. (5.4)**
- **Prolonged use of Meperidine Hydrochloride Tablets or Oral Solution 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. (5.5)**
- **Concomitant use with CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) can result in fatal overdose of meperidine. (5.6, 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. (5.7, 7)**
- **Concomitant use of Meperidine Hydrochloride Tablets or Oral Solution with monoamine oxidase inhibitors (MAOIs) can result in coma, severe respiratory depression, cyanosis and hypotension. Use of Meperidine Hydrochloride Tablets or Oral Solution with MAOIs within the last 14 days is contraindicated. (4, 5.8, 6)**

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

Dosage and Administration (2.2) 03/2021

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

Meperidine Hydrochloride 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 (1):

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, reserve Meperidine Hydrochloride Tablets and Oral Solution 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 severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse. (2.1)
- Discuss availability of naloxone with the patient and caregiver and assess each patient's need for access to naloxone, both when initiating and renewing treatment with Meperidine Hydrochloride Tablets or Oral Solution. Consider prescribing naloxone based on the patient's risk factors for overdose. (2.2, 5.2, 5.4, 5.7)
- *Adult Patients:* Initiate treatment in adults with 50 mg to 150 mg every 3 to 4 hours as needed for pain. (2.3)
- *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. (2.3)
- Do not abruptly discontinue Meperidine Hydrochloride Tablets or Oral Solution in a physically dependent patient because rapid discontinuation of opioid analgesics has resulted in serious withdrawal symptoms, uncontrolled pain, and suicide. (2.6)

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

Tablets: 50 mg and 100 mg. (3)

Oral Solution: 50 mg per 5 mL. (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. (5.9)
- *Serotonin Syndrome:* Potentially life-threatening condition could result from concomitant serotonergic drug administration. Discontinue Meperidine Hydrochloride Tablets or Oral Solution if serotonin syndrome is suspected. (5.10)
- *Adrenal Insufficiency:* If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.11)
- *Severe Hypotension:* Monitor during dosage initiation and titration. Avoid use of Meperidine Hydrochloride Tablets or Oral Solution in patients with circulatory shock. (5.12)
- *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 or Oral Solution in patients with impaired consciousness or coma. (5.13)

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

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

To report SUSPECTED ADVERSE REACTIONS, contact West-Ward Pharmaceuticals Corp. at 1-

DRUG INTERACTIONS

- *Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics:* Avoid use with Meperidine Hydrochloride Tablets or Oral Solution because they may reduce analgesic effect of meperidine 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: 3/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

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Risk of Medication Errors

Ensure accuracy when prescribing, dispensing, and administering Meperidine Hydrochloride 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

Meperidine Hydrochloride Tablets and Oral Solution expose 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, and monitor all patients regularly for the development of these behaviors and conditions [see *Warnings and Precautions (5.2)*].

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 REMS for these products [see *Warnings and Precautions (5.3)*]. 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:

- complete a REMS-compliant education program,
- counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,
- emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and
- consider other tools to improve patient, household, and community safety.

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of Meperidine Hydrochloride Tablets or Oral Solution. Monitor for respiratory depression, especially during initiation of Meperidine Hydrochloride Tablets or Oral Solution or following a dose increase [see *Warnings and Precautions (5.4)*].

Accidental Ingestion

Accidental ingestion of Meperidine Hydrochloride Tablets or Oral Solution, especially by children, can result in a fatal overdose of meperidine [see Warnings and Precautions (5.4)].

Neonatal Opioid Withdrawal Syndrome

Prolonged use of Meperidine Hydrochloride Tablets or Oral Solution 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 (5.5)].

Cytochrome P450 3A4 (CYP3A4) Interaction

The concomitant use of Meperidine Hydrochloride 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 Meperidine Hydrochloride Tablets or Oral Solution and any CYP3A4 inhibitor or inducer [see Warnings and Precautions (5.6), 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 (5.7), Drug Interactions (7)].

- **Reserve concomitant prescribing of Meperidine Hydrochloride Tablets or Oral Solution 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 or Oral Solution with Monoamine Oxidase Inhibitors (MAOIs)

Concomitant use of meperidine hydrochloride with monoamine oxidase inhibitors (MAOIs) can result in coma, severe respiratory depression, cyanosis, and hypotension. Use of Meperidine Hydrochloride 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

Meperidine Hydrochloride 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, and misuse with opioids, even at recommended doses [see *Warnings and Precautions (5.2)*], reserve Meperidine Hydrochloride Tablets and Oral Solution 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 or Oral Solution should not be used for treatment of chronic pain. Prolonged meperidine 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

Ensure accuracy when prescribing, dispensing, and administering Meperidine Hydrochloride Oral Solution to avoid dosing errors due to confusion between mg and mL, and with other Meperidine Hydrochloride Oral 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.

Do not use household teaspoons or tablespoons to measure Meperidine Hydrochloride Oral Solution, as using a tablespoon instead of a teaspoon could lead to overdosage.

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

Dilute each dose of Meperidine Hydrochloride Oral Solution in one-half glass of water because the undiluted solution may exert a slight topical anesthetic effect on mucous membranes.

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 (5.2)*].

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 or Meperidine Hydrochloride Oral Solution and adjust the dosage accordingly [see *Warnings and Precautions (5.4)*].

2.2 Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose

Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Meperidine Hydrochloride Tablets or Oral Solution [see *Warnings and Precautions (5.4)*, *Patient Counseling Information (17)*].

Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (e.g., by prescription, directly from a pharmacist, or as part of a community-based program).

Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient [see *Warnings and Precautions (5.2, 5.4, 5.7)*].

Consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose.

2.3 Initial Dosage

Adults:

Initiate treatment with Meperidine Hydrochloride Tablets or Oral Solution in a dosing range of 50 mg to 150 mg (5 mL to 15 mL) orally, every 3 or 4 hours as needed for pain.

Pediatric Patients:

Initiate treatment with Meperidine Hydrochloride Tablets or Oral Solution 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.

2.4 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.

2.5 Titration and Maintenance of Therapy

Individually titrate Meperidine Hydrochloride Tablets or 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 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 (5.2)*]. 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 meperidine 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.

2.6 Safe Reduction or Discontinuation of Meperidine Hydrochloride Tablets or Oral Solution

Do not abruptly discontinue Meperidine Hydrochloride Tablets or Oral Solution in patients who may be physically dependent on opioids. Rapid discontinuation of opioid analgesics in patients who are physically dependent on opioids has resulted in 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. 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 Meperidine Hydrochloride Tablets or Oral Solution, there are a variety of factors that should be considered, including the dose of Meperidine Hydrochloride Tablets or 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 Meperidine Hydrochloride Tablets or 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, monitor 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 a long duration 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

Meperidine Hydrochloride Tablets USP:

- 50 mg tablet is supplied as a white, round tablet, scored on one side with “54 879” debossed on the other side.
- 100 mg tablet is supplied as a white, round tablet, scored on one side with “54 163” debossed on the other side.

Meperidine Hydrochloride Oral Solution USP:

- 50 mg/5 mL oral solution: clear, colorless, slightly viscous solution.

4 CONTRAINDICATIONS

Meperidine Hydrochloride Tablets and Oral Solution are contraindicated in patients with:

- Significant respiratory depression [*see Warnings and Precautions (5.4)*].
- 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 (5.14)*].
- Hypersensitivity to meperidine or to any of the 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 Meperidine Oral Solution. Ensure that the dose is communicated clearly and dispensed accurately.

Do not use a teaspoon or a tablespoon to measure a dose. A household teaspoon is not an adequate measuring device. Given the inexactitude of the household spoon measure and the risk of mistakenly using a tablespoon instead of a teaspoon, which could lead to overdosage, it is strongly recommended that caregivers obtain and use a calibrated measuring device. Healthcare providers should recommend a calibrated device that can measure and deliver the prescribed dose accurately, and instruct caregivers to use extreme caution in measuring the dosage [*see Dosage and Administration (2.1)*].

5.2 Addiction, Abuse, and Misuse

Meperidine Hydrochloride Tablets and Oral Solution contain meperidine, a Schedule II controlled substance. As an opioid, meperidine 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 or Oral Solution. 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 or Oral Solution, and monitor all patients receiving Meperidine Hydrochloride 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 Meperidine Hydrochloride Tablets or Oral Solution, but use in such patients necessitates intensive counseling about the risks and proper use of Meperidine Hydrochloride Tablets or Oral Solution along with intensive monitoring for signs of addiction, abuse, and misuse. Consider prescribing naloxone for the emergency treatment of opioid overdose [*see Dosage and Administration (2.2), Warnings and Precautions (5.4)*].

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 or Oral Solution. 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.

5.3 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 Healthcare 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 medicines 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 800-503-0784, or log on to www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

5.4 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 (CO₂) 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, 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 or Oral Solution.

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

Accidental ingestion of even one dose of Meperidine Hydrochloride Tablets or Oral Solution, especially by children, can result in respiratory depression and death due to an overdose of Meperidine Hydrochloride Tablets or Oral Solution.

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 *Patient Counseling Information (17)*].

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 Naloxone for the Emergency Treatment of Opioid Overdose

Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Meperidine Hydrochloride Tablets and Oral Solution. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (e.g., by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered [see *Patient Counseling Information (17)*].

Consider prescribing naloxone, based on the patient's risk factors for overdose, such

as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone [see *Warnings and Precautions (5.2, 5.7, Patient Counseling Information (17))*].

5.5 Neonatal Opioid Withdrawal Syndrome

Prolonged use of Meperidine Hydrochloride Tablets or Oral Solution 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)*].

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

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

Concomitant use of Meperidine Hydrochloride 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 Meperidine Hydrochloride Tablets or Oral Solution 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)*].

5.7 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 or Oral Solution with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine

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.

If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose [see *Dosage and Administration (2.2)*, *Warnings and Precautions (5.4)*].

Advise both patients and caregivers about the risks of respiratory depression and sedation when Meperidine Hydrochloride 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)*, *Patient Counseling Information (17)*].

5.8 Fatal Interaction with Monoamine Oxidase Inhibitors (MAOIs)

Meperidine Hydrochloride Tablets or Oral Solution 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 or Oral Solution 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.

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

The use of Meperidine Hydrochloride 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:

Meperidine-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 [see *Warnings and Precautions (5.4)*].

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 (5.4)*].

Monitor such patients closely, particularly when initiating and titrating Meperidine Hydrochloride Tablets or Oral Solution and when meperidine is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients.

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 meperidine hydrochloride with serotonergic drugs. Serotonergic drugs include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT₃ receptor antagonists, drugs that affect the serotonergic neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (i.e., cyclobenzaprime, 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). 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 or Oral Solution if serotonin syndrome is suspected.

5.11 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.

5.12 Severe Hypotension

Meperidine 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 or Oral Solution. In patients with circulatory shock, meperidine may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of meperidine in patients with circulatory shock.

5.13 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 CO₂ retention (e.g., those with evidence of increased intracranial pressure or brain tumors), meperidine may reduce respiratory drive, and the resultant CO₂ retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Meperidine Hydrochloride Tablets or Oral Solution.

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

5.14 Risks of Use in Patients with Gastrointestinal Conditions

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

The meperidine in Meperidine Hydrochloride Tablets and Oral Solution 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.

5.15 Increased Risk of Seizures in Patients with Seizure Disorders

The meperidine in Meperidine Hydrochloride Tablets and Oral Solution 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 seizure disorders. Monitor patients with a history of seizure disorders for worsened seizure control during meperidine

therapy. Prolonged meperidine use may increase the risk of toxicity (e.g., seizures) from the accumulation of the meperidine metabolite, normeperidine.

5.16 Withdrawal

Do not abruptly discontinue Meperidine Hydrochloride Tablets and Oral Solution in a patient physically dependent on opioids. When discontinuing Meperidine Hydrochloride Tablets and 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 Meperidine Hydrochloride 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)*].

5.17 Risks of Driving and Operating Machinery

Meperidine 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 or Oral Solution and know how they will react to the medication [see *Patient Counseling Information (17)*].

5.18 Risks in Patients with Pheochromocytoma

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

5.19 Risk of Use in Patients with Atrial Flutter and Other Supraventricular Tachycardia

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 (5.4)*]
- Neonatal Opioid Withdrawal Syndrome [see *Warnings and Precautions (5.5)*]
- Interactions with Benzodiazepines or Other CNS Depressants [see *Warnings and Precautions (5.7)*]
- Serotonin Syndrome [see *Warnings and Precautions (5.10)*]
- Adrenal Insufficiency [see *Warnings and Precautions (5.11)*]
- Severe Hypotension [see *Warnings and Precautions (5.12)*]

- Gastrointestinal Adverse Reactions [see *Warnings and Precautions (5.14)*]
- Seizures [see *Warnings and Precautions (5.15)*]
- Withdrawal [see *Warnings and Precautions (5.16)*]

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 (5.8)*], 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)*].

To report SUSPECTED ADVERSE REACTIONS, contact West-Ward Pharmaceuticals Corp. at 1-800-962-8364 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

7 DRUG INTERACTIONS

Table 1 includes clinically significant drug interactions with meperidine.

Table 1: Clinically Significant Drug Interactions with Meperidine Hydrochloride Tablets and Oral Solution

Monoamine Oxidase Inhibitors (MAOIs)	
<i>Clinical Impact:</i>	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.
<i>Intervention:</i>	Do not use Meperidine Hydrochloride Tablets or Oral Solution 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.
<i>Examples:</i>	Phenelzine, tranylcypromine, linezolid.
Inhibitors of CYP3A4 and CYP2B6	
<i>Clinical Impact:</i>	The concomitant use of meperidine 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 and CYP2B6 and CYP3A4 inhibitors, particularly when an inhibitor is added after a stable dose of meperidine is achieved [see <i>Warnings and Precautions (5.6)</i>]. After stopping a CYP3A4 or CYP2B6 inhibitor, as the effects of the inhibitor decline, the meperidine plasma concentration will decrease [see <i>Clinical Pharmacology (12.3)</i>], resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to meperidine.
<i>Intervention:</i>	If concomitant use is necessary, consider dosage reduction of Meperidine Hydrochloride Tablets or Oral Solution 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 dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal.
<i>Examples:</i>	Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), protease inhibitors (e.g., ritonavir).
CYP3A4 and CYP2B6 Inducers	

<i>Clinical Impact:</i>	The concomitant use of meperidine and CYP3A4 or CYP2B6 inducers can decrease the plasma concentration of meperidine [see <i>Clinical Pharmacology (12.3)</i>], resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to meperidine [see <i>Warnings and Precautions (5.6)</i>]. After stopping a CYP3A4 or CYP2B6 inducer, as the effects of the inducer decline, the meperidine plasma concentration will increase [see <i>Clinical Pharmacology (12.3)</i>], which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression.
<i>Intervention:</i>	If concomitant use is necessary, consider increasing the Meperidine Hydrochloride Tablets or Oral Solution dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal. If a CYP3A4 or CYP2B6 inducer is discontinued, consider meperidine dosage reduction and monitor for signs of respiratory depression.
<i>Examples:</i>	Rifampin, carbamazepine, phenytoin.
Benzodiazepines and Other Central Nervous System (CNS) Depressants	
<i>Clinical Impact:</i>	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.
<i>Intervention:</i>	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. If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose [see <i>Dosage and Administration (2.2, 2.4)</i> , <i>Warnings and Precautions (5.2, 5.4, 5.7)</i>].
<i>Examples:</i>	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.
Serotonergic Drugs	
<i>Clinical Impact:</i>	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome [see <i>Warnings and Precautions (5.10)</i>].
<i>Intervention:</i>	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue Meperidine Hydrochloride Tablets or Oral Solution if serotonin syndrome is suspected.
<i>Examples:</i>	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT ₃ receptor antagonists, drugs that affect 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	
<i>Clinical Impact:</i>	May reduce the analgesic effect of meperidine and/or precipitate

	withdrawal symptoms.
<i>Intervention:</i>	Avoid concomitant use.
<i>Examples:</i>	Butorphanol, nalbuphine, pentazocine, buprenorphine.
Muscle Relaxants	
<i>Clinical Impact:</i>	Meperidine Hydrochloride Tablets or Oral Solution may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
<i>Intervention:</i>	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of Meperidine Hydrochloride Tablets or 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 prescribing naloxone for the emergency treatment of opioid overdose [see <i>Dosage and Administration (2.2)</i> , <i>Warnings and Precautions (5.4, 5.7)</i>].
Diuretics	
<i>Clinical Impact:</i>	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
<i>Intervention:</i>	Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Anticholinergic Drugs	
<i>Clinical Impact:</i>	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
<i>Intervention:</i>	Monitor patients for signs of urinary retention or reduced gastric motility when Meperidine Hydrochloride Tablets or Oral Solution is used concomitantly with anticholinergic drugs.
Acyclovir	
<i>Clinical Impact:</i>	The concomitant use of acyclovir may increase the plasma concentrations of meperidine and its metabolite, normeperidine.
<i>Intervention:</i>	If concomitant use of acyclovir and Meperidine Hydrochloride Tablets or Oral Solution is necessary, monitor patients for respiratory depression and sedation at frequent intervals.
Cimetidine	
<i>Clinical Impact:</i>	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.
<i>Intervention:</i>	If concomitant use cimetidine and Meperidine Hydrochloride Tablets or Oral Solution 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 (5.5)*]. Available data with meperidine is 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 1,200 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 (5.5)*].

Labor and 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 antagonist, such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate. Meperidine is not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate. Opioid analgesics, including meperidine, 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 1,200 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 and any potential adverse effects on the breastfed infant from Meperidine Hydrochloride Tablets or Oral Solution or from the underlying maternal condition.

Clinical Considerations:

Monitor infants exposed to meperidine 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 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 or Oral Solution slowly in geriatric patients and monitor closely for signs of central nervous system and respiratory depression [see *Warnings and Precautions (5.7, 5.9)*].

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

9.2 Abuse

Meperidine Hydrochloride Tablets and Oral Solution 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 can be abused and is subject to misuse, addiction, and criminal diversion [see *Warnings and Precautions (5.2)*].

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 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 Meperidine Hydrochloride Tablets and Oral Solution:

Meperidine Hydrochloride Tablets and Oral Solution are for oral use only. Abuse of meperidine 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 with alcohol and other central nervous system depressants. Due to the presence of talc as one of the excipients in tablets, parenteral drug abuse of crushed tablets can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart disease. 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 is a physiological state in which the body adapts to the drug after a period of regular exposure, resulting 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.

Do not abruptly discontinue Meperidine Hydrochloride Tablets and Oral Solution in a patient physically dependent on opioids. Rapid tapering of Meperidine Hydrochloride 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 Meperidine Hydrochloride Tablets and Oral Solution, gradually taper the dosage using a patient-specific plan that considers the following: the dose of Meperidine Hydrochloride 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 a long duration 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) and Warnings (5.16)*].

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, 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.

Opioid antagonists, such as naloxone, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to opioid overdose, administer an opioid antagonist.

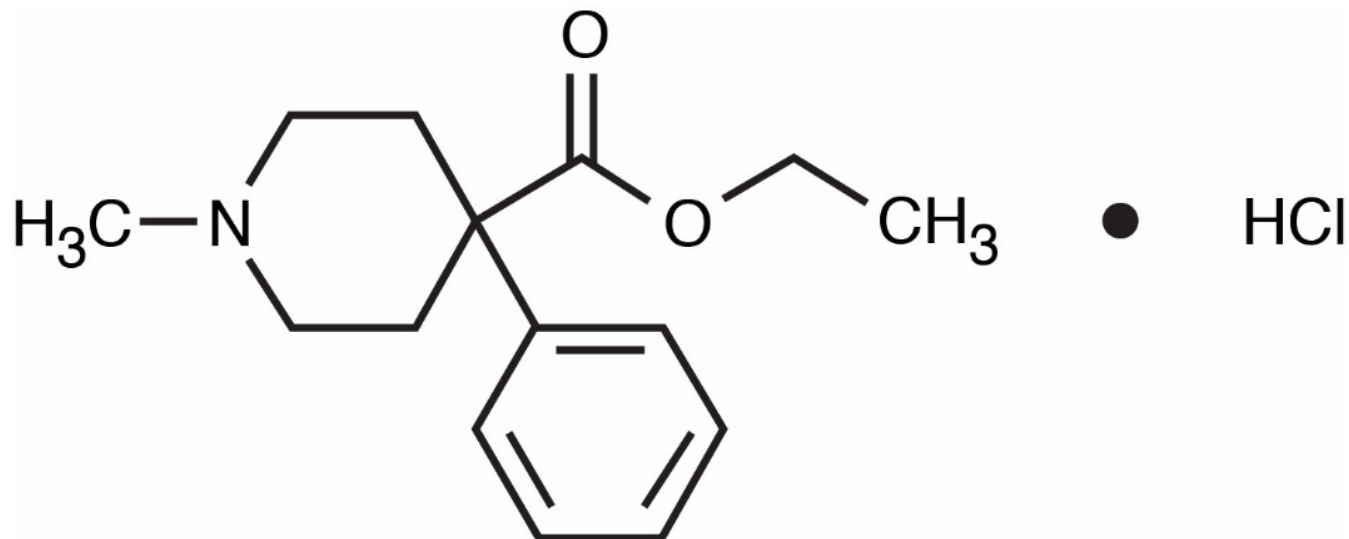
Because the duration of opioid reversal is expected to be less than the duration of action of meperidine in Meperidine Hydrochloride Tablets or Oral Solution, carefully monitor the patient until spontaneous respiration is reliably reestablished. If the response to an opioid antagonist is suboptimal or 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 is an opioid agonist, available as 50 mg and 100 mg tablets or 50 mg per 5 mL solution 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 $C_{15}H_{21}NO_2 \cdot HCl$, and it has the following chemical structure:



Meperidine hydrochloride USP is a fine, white powder with a melting point of 186° C to 189° C. It is very soluble in water and has a neutral reaction. The solution is not decomposed by a short period of boiling.

Each Meperidine Hydrochloride Tablet USP for oral administration contains either 50 mg or 100 mg meperidine hydrochloride USP and the following inactive ingredients: corn starch, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and pregelatinized starch.

Each 5 mL of Meperidine Hydrochloride Oral Solution USP for oral administration contains 50 mg meperidine hydrochloride USP and the following inactive ingredients: glycerin, hydrochloric acid, maltol, sodium benzoate, sorbitol solution and purified water.

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 tablet is supplied as a white, round tablet, scored on one side with “54 879” debossed on the other side.

NDC 0054-8595-11: 1 x 25 Unit-Dose (Reverse Numbered) Tablets

NDC 0054-4595-25: Bottle of 100 Tablets

100 mg tablet is supplied as a white, round tablet, scored on one side with “54 163” debossed on the other side.

NDC 0054-4596-25: Bottle of 100 Tablets

Meperidine Hydrochloride Oral Solution USP

50 mg per 5 mL oral solution is supplied as a clear, colorless, slightly viscous (unflavored) solution.

NDC 0054-3545-63: Bottle of 500 mL

Dispense in a tight, light-resistant container as defined in the USP/NF.

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

Store Meperidine Hydrochloride Tablets or Oral Solution securely and dispose of properly [see *Patient Counseling*

Information (17)].

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 Meperidine Hydrochloride Tablets or Oral Solution securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home [see *Warnings and Precautions (5.1, 5.2), Abuse (9.2)*]. Inform patients that leaving Meperidine Hydrochloride Tablets or Oral Solution unsecured can pose a deadly risk to others in the home.

Advise patients and caregivers that when medicines are no longer needed, they should be disposed of promptly. Expired, unwanted, or unused Meperidine Hydrochloride Tablets or 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:

Provide detailed instructions to patients on how to measure and take the correct dose of Meperidine Hydrochloride Oral Solution to ensure that the dose is measured and administered accurately [see *Warnings and Precautions (5.1)*].

If the prescribed dosage is changed, instruct patients 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 Meperidine Hydrochloride 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 Meperidine Hydrochloride Tablets or Oral Solution with others and to take steps to protect meperidine 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 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)*].

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose

Discuss with the patient and caregiver the availability of naloxone for the emergency treatment of opioid overdose, both when initiating and renewing treatment with Meperidine Hydrochloride Tablets and Oral Solution. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (e.g., by prescription, directly from a pharmacist, or as part of a community-based program) [see *Dosage and Administration (2.2)*, *Warnings 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 naloxone's effects 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 naloxone is administered [see *Overdosage (10)*].

If naloxone is prescribed, also advise patients and caregivers:

- How to treat with naloxone in the event of an opioid overdose
- To tell family and friends about their naloxone 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 naloxone. Emphasize the importance of doing this before an opioid emergency

happens, so the patient and caregiver will know what to do.

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 Meperidine Hydrochloride Tablets or Oral Solution is 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 (5.7)*, *Drug Interactions (7)*].

MAOI Interaction:

Inform patients not to take Meperidine Hydrochloride Tablets or Oral Solution while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking meperidine [see *Warnings and Precautions (5.8)*, *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 (5.10)*, *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 (5.11)*].

Important Administration Instructions:

Instruct patients how to properly take Meperidine Hydrochloride Tablets or Oral Solution.

- Advise patients never to use a household teaspoon or tablespoon to measure Meperidine Hydrochloride Oral Solution.
- Advise patients not to adjust the dose of Meperidine Hydrochloride Tablets or Oral Solution without consulting with a physician or other healthcare professional.
- Advise patients to dilute each dose of Meperidine Hydrochloride 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 Meperidine Hydrochloride Tablets or Oral Solution without first discussing a tapering plan with the prescriber [see *Dosage and Administration (2.6)*].

Hypotension:

Inform patients that meperidine 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 (5.12)*].

Anaphylaxis:

Inform patients that anaphylaxis has been reported with ingredients contained in Meperidine Hydrochloride Tablets or 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 prolonged use of meperidine 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 meperidine 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 or 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)*].

Distr. by: **West-Ward**

Pharmaceuticals Corp.

Eatontown, NJ 07724

10003964/13

Revised March 2021

MEDICATION GUIDE

**Meperidine Hydrochloride Tablets USP CII
and
Meperidine Hydrochloride Oral Solution USP CII
(me per' i deen hye" droe klor' ide)
Rx only**

Meperidine Hydrochloride 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 Meperidine Hydrochloride Tablets and Oral Solution:

- **Get emergency help or call 911 right away if you take too much Meperidine Hydrochloride Tablets or Oral Solution (overdose).** When you first start taking Meperidine Hydrochloride 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. Talk to your healthcare provider about naloxone, a medicine for the emergency treatment of an opioid overdose.
- Taking Meperidine Hydrochloride Tablets or Oral Solution 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 or Oral Solution. They could die from taking it. Selling or giving away Meperidine Hydrochloride Tablets or Oral Solution is against the law.
- Store Meperidine Hydrochloride Tablets or Oral Solution securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home.

Do not take Meperidine Hydrochloride Tablets or Oral Solution if you have:

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

Before taking Meperidine Hydrochloride Tablets or 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:

- **Pregnant or planning to become pregnant.** Prolonged use of Meperidine Hydrochloride Tablets or Oral Solution 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.
- 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 Meperidine Hydrochloride Tablets or Oral Solution with certain other medicines can cause serious side effects that could lead to death.

When taking Meperidine Hydrochloride Tablets or Oral Solution:

- Do not change your dose. Take Meperidine Hydrochloride Tablets or Oral Solution exactly as prescribed by your healthcare provider. Use the lowest dose possible for the shortest time needed.
- Always use a calibrated measuring device for Meperidine Hydrochloride Oral Solution to correctly measure your dose. Never use a household teaspoon or tablespoon to measure Meperidine Hydrochloride Oral Solution.
- Mix each dose of Meperidine Hydrochloride Oral Solution into one-half glass of water before swallowing.
- Take your prescribed dose every 3 to 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 or Oral Solution regularly, do not stop taking Meperidine Hydrochloride Tablets or Oral Solution without talking to your healthcare provider.
- Dispose of expired, unwanted, or unused Meperidine Hydrochloride Tablets or 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 Meperidine Hydrochloride Tablets or Oral Solution DO NOT:

- Drive or operate heavy machinery, until you know how Meperidine Hydrochloride Tablets or Oral Solution affects 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 or Oral Solution may cause you to overdose and die.

The possible side effects of Meperidine Hydrochloride Tablets or 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 Meperidine Hydrochloride Tablets and Oral Solution. 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.**

For information, please call West-Ward Pharmaceuticals Corp. at 1-800-962-8364.

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

Distr. by: **West-Ward**

Pharmaceuticals Corp.

Eatontown, NJ 07724

10003964/13

Revised March 2021

PACKAGE/LABEL PRINCIPAL DISPLAY PANEL

Meperidine Hydrochloride Tablets USP, 50 mg

NDC 0054-4595-25

Rx only

Each tablet contains 50 mg
meperidine hydrochloride
USP.

USUAL DOSAGE: See
Package Insert for Complete
Prescribing Information.

Dispense in a tight,
light-resistant container as
defined in the USP/NF.

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

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NDC 0054-4595-25

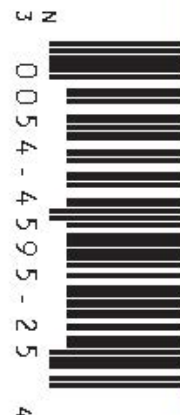
100 Tablets

**Meperidine
Hydrochloride** 
Tablets USP
50 mg

PHARMACIST: Dispense the attached
Medication Guide to each patient.

R_x only

 **WEST-WARD**
A NIKMA COMPANY



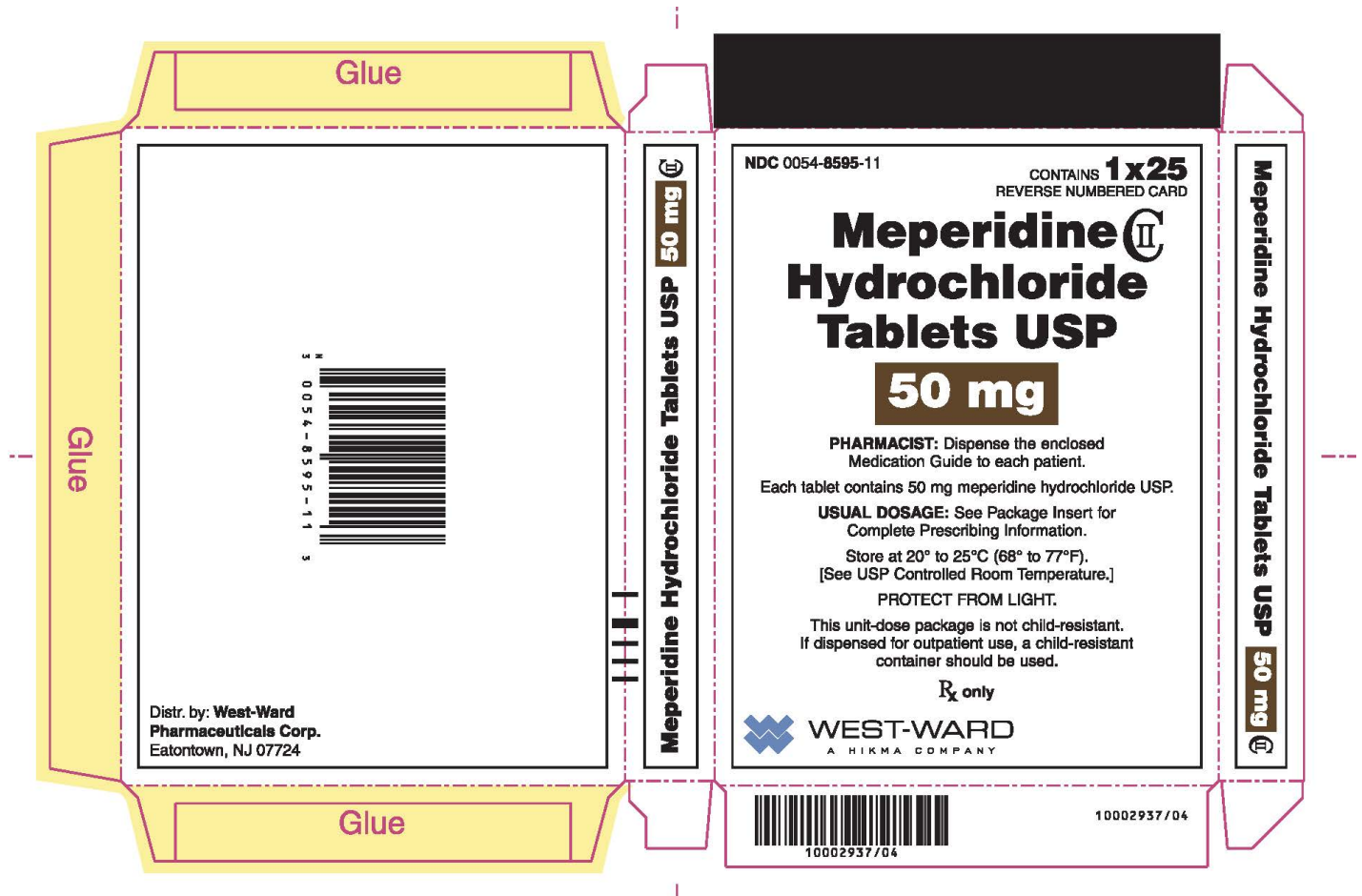
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PACKAGE/LABEL PRINCIPAL DISPLAY PANEL

Meperidine Hydrochloride Tablets USP, 50 mg

NDC 0054-8595-11

Rx only



PACKAGE/LABEL PRINCIPAL DISPLAY PANEL

Meperidine Hydrochloride Tablets USP, 100 mg

NDC 0054-4596-25

Rx only

Each tablet contains
100 mg meperidine
hydrochloride USP.

USUAL DOSAGE:
See Package Insert for
Complete Prescribing
Information.

Dispense in a tight,
light-resistant container
as defined in the
USP/NF.

Distr. by: **West-Ward
Pharmaceuticals Corp.**
Eatontown, NJ 07724

NDC 0054-4596-25 100 Tablets

Meperidine [Ⓜ] Hydrochloride Tablets USP

100 mg

PHARMACIST: Dispense
the attached Medication Guide
to each patient.

R_x only



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



4179270//06

PACKAGE/LABEL PRINCIPAL DISPLAY PANEL

Meperidine Hydrochloride Oral Solution USP, 50 mg per 5 mL

NDC 0054-3545-63

Rx only

Ingredient Name	Basis of Strength	Strength
MEPERIDINE HYDROCHLORIDE (UNII: N8E7F7Q170) (MEPERIDINE - UNII:9E338QE28F)	MEPERIDINE HYDROCHLORIDE	50 mg

Inactive Ingredients

Ingredient Name	Strength
STARCH, CORN (UNII: O8232NY3SJ)	
CROSCARMELOSE SODIUM (UNII: M28OL1HH48)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
POVIDONE, UNSPECIFIED (UNII: FZ989GH94E)	

Product Characteristics

Color	WHITE	Score	2 pieces
Shape	ROUND	Size	6mm
Flavor		Imprint Code	54;879
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0054-4595-25	100 in 1 BOTTLE; Type 0: Not a Combination Product	03/12/1997	08/23/2021

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA040110	03/12/1997	08/23/2021

MEPERIDINE HYDROCHLORIDE

meperidine hydrochloride tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0054-8595
Route of Administration	ORAL	DEA Schedule	CII

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
MEPERIDINE HYDROCHLORIDE (UNII: N8E7F7Q170) (MEPERIDINE - UNII:9E338QE28F)	MEPERIDINE HYDROCHLORIDE	50 mg

Inactive Ingredients

Ingredient Name	Strength
STARCH, CORN (UNII: O8232NY3SJ)	
CROSCARMELOSE SODIUM (UNII: M28OL1HH48)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
POVIDONE, UNSPECIFIED (UNII: FZ989GH94E)	

Product Characteristics

Color	WHITE	Score	2 pieces
Shape	ROUND	Size	6mm
Flavor		Imprint Code	54;879
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0054-8595-11	1 in 1 BOX	03/12/1997	08/23/2021
1		25 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA040110	03/12/1997	08/23/2021

MEPERIDINE HYDROCHLORIDE

meperidine hydrochloride tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0054-4596
Route of Administration	ORAL	DEA Schedule	CII

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
MEPERIDINE HYDROCHLORIDE (UNII: N8E7F7Q170) (MEPERIDINE - UNII:9E338QE28F)	MEPERIDINE HYDROCHLORIDE	100 mg

Inactive Ingredients

Ingredient Name	Strength
STARCH, CORN (UNII: O8232NY3SJ)	
CROSCARMELOSE SODIUM (UNII: M28OL1HH48)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
POVIDONE, UNSPECIFIED (UNII: FZ989GH94E)	

Product Characteristics

Color	WHITE	Score	2 pieces
Shape	ROUND	Size	8mm
Flavor		Imprint Code	54;163
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0054-4596-25	100 in 1 BOTTLE; Type 0: Not a Combination Product	03/12/1997	08/23/2021

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA040110	03/12/1997	08/23/2021

MEPERIDINE HYDROCHLORIDE

meperidine hydrochloride solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0054-3545
Route of Administration	ORAL	DEA Schedule	CII

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
MEPERIDINE HYDROCHLORIDE (UNII: N8E7F7Q170) (MEPERIDINE - UNII:9E338QE28F)	MEPERIDINE HYDROCHLORIDE	50 mg in 5 mL

Inactive Ingredients

Ingredient Name	Strength
GLYCERIN (UNII: PDC6A3C0OX)	
HYDROCHLORIC ACID (UNII: QTT17582CB)	

MALTOL (UNII: 3A9RD92BS4)	
SODIUM BENZOATE (UNII: OJ245FE5EU)	
SORBITOL (UNII: 506T60A25R)	
WATER (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0054-3545-63	500 mL in 1 BOTTLE; Type 0: Not a Combination Product	01/30/1985	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA088744	01/30/1985	

Labeler - West-Ward Pharmaceuticals Corp. (080189610)

Establishment

Name	Address	ID/FEI	Business Operations
West-Ward Columbus Inc.		058839929	MANUFACTURE(0054-4595, 0054-8595, 0054-4596, 0054-3545)

Revised: 3/2021

West-Ward Pharmaceuticals Corp.