MEPERIDINE HYDROCHLORIDE- meperidine hydrochloride injection, solution
Hospira, Inc.

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MEPERIDINE
Hydrochloride
Injection, USP

300 mg (10 mg/mL)

ONLY FOR USE WITH A COMPATIBLE HOSPIRA PCA PUMP SET WITH INJECTOR AND A
COMPATIBLE HOSPIRA INFUSION DEVICE.

CII

Rx only
Addiction, Abuse, and Misuse

Meperidine Hydrochloride Injection exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Meperidine Hydrochloride Injection, and monitor all patients regularly for the development of these behaviors and conditions [see WARNINGS].

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of Meperidine Hydrochloride Injection. Monitor for respiratory depression, especially during initiation of Meperidine Hydrochloride Injection or following a dose increase [see WARNINGS].

Neonatal Opioid Withdrawal Syndrome

Prolonged use of Meperidine Hydrochloride Injection 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].

Cytochrome P450 3A4 Interaction

The concomitant use of Meperidine Hydrochloride Injection with all cytochrome P450 3A4 inhibitors may result in an increase in meperidine plasma concentrations, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in meperidine plasma concentration. Monitor patients receiving Meperidine Hydrochloride Injection and any CYP3A4 inhibitor or inducer [see CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS; Drug Interactions].

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, PRECAUTIONS; Drug Interactions].

- Reserve concomitant prescribing of meperidine hydrochloride 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 Injection with Monoamine oxidase (MAO) inhibitors

Concomitant use of Meperidine Hydrochloride Injection with monoamine oxidase (MAO) inhibitors can result in coma, severe respiratory depression, cyanosis and hypotension. Use of Meperidine Hydrochloride Injection with MAO inhibitors within the last 14 days is contraindicated [see CONTRAINDICATIONS, WARNINGS, PRECAUTIONS; Drug Interactions].
DESCRIPTION

Meperidine Hydrochloride Injection, USP 10 mg/mL is a sterile, nonpyrogenic, hypotonic solution of meperidine hydrochloride, USP, in an acetate buffer. This product is to be administered by the intravenous route via a compatible Hospira infusion device.

Each mL contains meperidine hydrochloride 10 mg. Sodium acetate, anhydrous 1.5 mg and glacial acetic acid, 0.0012 mL are added as buffers. pH 4.5 (3.5 to 6.0).

The solution contains no bacteriostat or antimicrobial agent and is intended only for use as a single-dose unit to provide analgesia via the intravenous route using a compatible Hospira infusion device.

Meperidine is classified pharmacologically as a synthetic narcotic analgesic.

Meperidine Hydrochloride is ethyl-1-methyl-4-phenylisonipecotate hydrochloride, a white, crystalline substance with a melting point of 186° to 189°C. It is readily soluble in water and has a neutral reaction and a slightly bitter taste. The solution is not decomposed by a short period of boiling.

It has the following structural formula:

\[
\begin{align*}
\text{C}_15\text{H}_21\text{N}_2\text{O}_2 \cdot \text{HCl} & \quad \text{M.W. 283.80} \\
\end{align*}
\]

CLINICAL PHARMACOLOGY

Meperidine hydrochloride is a narcotic analgesic 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.

There is some evidence which suggests that meperidine may produce less smooth muscle spasm, constipation, and depression of the cough reflex than equianalgesic doses of morphine. Meperidine, in 60 mg to 80 mg parenteral doses, is approximately equivalent in analgesic effect to 10 mg of morphine. The onset of action is slightly more rapid than with morphine, and the duration of action is slightly shorter. Meperidine is significantly less effective by the oral than by the parenteral route, but the exact ratio of oral to parenteral effectiveness is unknown.

Meperidine is metabolized through biotransformation. The elimination half-life is 3 to 8 hours in healthy volunteers and is 1.3 to 2 times greater in post-operative or cirrhotic patients. The only bioactive metabolite is normeperidine which has an average elimination half-life of 20.6 hours. Elevated serum levels have been reported to cause central nervous system excitatory effects.

Effects on the Endocrine System

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to hormonal changes 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
INDICATIONS AND USAGE
Meperidine Hydrochloride Injection is indicated for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

Limitations of Use
Meperidine Hydrochloride Injection should not be used for treatment of chronic pain. Prolonged Meperidine Hydrochloride Injection use may increase the risk of toxicity (e.g., seizures) from the accumulation of the meperidine metabolite, normeperidine.

Because of the risks of addiction, abuse, and misuse, with opioids, even at recommended doses [see WARNINGS], reserve meperidine hydrochloride 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

CONTRAINDICATIONS
Meperidine Hydrochloride Injection is contraindicated in patients with:
- Significant respiratory depression [see WARNINGS]
- Acute of severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment [see WARNINGS]
- Concomitant use of monoamine oxidase (MAO) inhibitors or within 14 days of having taken an MAOI [see WARNINGS, PRECAUTIONS; Drug Interactions]
- Known of suspected gastrointestinal obstruction, including paralytic ileus [see WARNINGS]
- Hypersensitivity to meperidine.

WARNINGS

Addiction, Abuse, and Misuse
Meperidine Hydrochloride Injection contains meperidine, a Schedule II controlled substance. As an opioid, Meperidine Hydrochloride Injection exposes users to the risks of addiction, abuse, and misuse [see DRUG ABUSE AND DEPENDENCE].

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed Meperidine Hydrochloride Injection. 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 Injection, and monitor all patients receiving Meperidine Hydrochloride Injection for the development of these behaviors or 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 Injection, but use in such patients necessitates intensive counseling about the risks and proper use of Meperidine Hydrochloride Injection along with intensive monitoring for signs of addiction, abuse, and misuse.

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing Meperidine Hydrochloride Injection. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity.
Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

**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]. 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 Hydrochloride Injection, 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 Injection.

To reduce the risk of respiratory depression, proper dosing and titration of Meperidine Hydrochloride Injection are essential [see DOSAGE AND ADMINISTRATION]. Overestimating the Meperidine Hydrochloride Injection dosage when converting patients from another opioid product can result in a fatal overdose with the first dose.

**Neonatal Opioid Withdrawal Syndrome**

Prolonged use of Meperidine Hydrochloride Injection 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 PRECAUTIONS; Information for Patients, Pregnancy].

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

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

Concomitant use of Meperidine Hydrochloride Injection with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease meperidine plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to meperidine. When using Meperidine Hydrochloride Injection with CYP3A4 inhibitors 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 [PRECAUTIONS; Drug Interactions, DOSAGE AND ADMINISTRATION].

**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 Injection 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 PRECAUTIONS; Drug Interactions].

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

Advise both patients and caregivers about the risks of respiratory depression and sedation when
Meperidine Hydrochloride Injection is used with benzodiazepines or other CNS depressants (including
alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of
concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients
for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for
overdose and death associated with the use of additional CNS depressants including alcohol and illicit
drugs [see PRECAUTIONS; Drug Interactions and PRECAUTIONS; Information for Patients].

**Fatal Interaction with Monoamine Oxidase Inhibitors**

Meperidine is contraindicated in patients who are receiving monoamine oxidase (MAO) inhibitors or
those who have recently received such agents. Therapeutic doses of meperidine have occasionally
precipitated unpredictable, severe, and occasionally fatal reactions in patients who have received such
agents within 14 days. The mechanism of these reactions is unclear, but may be related to a preexisting
hyperphenylalaninemia. Some have been characterized by coma, severe respiratory depression,
cyanosis, and hypotension, and have resembled the syndrome of acute 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 Injection in patients taking MAOIs or within 14 days of stopping
such treatment.

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

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

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

Patients with Chronic Pulmonary Disease

Meperidine Hydrochloride Injection - treated patients with significant chronic obstructive pulmonary
disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia,
hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive
including apnea, even at recommended dosages of Meperidine Hydrochloride Injection [see
Elderly, Cachetic, 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].

Monitor such patients closely, particularly when initiating and titrating Meperidine Hydrochloride Injection and when Meperidine Hydrochloride Injection is given concomitantly with other drugs that depress respiration [see WARNINGS]. Alternatively, consider the use of non-opioid analgesics in these patients.

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 Injection with serotonergic drugs. Serotonergic drugs include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonergic neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), and drugs that impair metabolism of serotonin (including MAO inhibitors, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue) [see PRECAUTIONS; Drug Interactions]. 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 Injection if serotonin syndrome is suspected.

Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than 1 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.

Hypotensive Effect

The administration of Meperidine Hydrochloride Injection may result in severe hypotension in the postoperative patient or any individual whose ability to maintain blood pressure has been compromised by a depleted blood volume or the administration of drugs such as the phenothiazines or certain anesthetics.

Head Injury and Increased Intracranial Pressure

The respiratory depressant effects of Meperidine Hydrochloride Injection and its capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a preexisting increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries. In such patients, Meperidine Hydrochloride Injection must be used with extreme caution and only if its use is deemed
Intravenous Use

See DOSAGE AND ADMINISTRATION.

Usage in Ambulatory Patients

Meperidine Hydrochloride Injection may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient should be cautioned accordingly.

Meperidine Hydrochloride Injection, like other narcotics, may produce orthostatic hypotension in ambulatory patients.

Usage in Pregnancy and Lactation

Meperidine Hydrochloride Injection should not be used in pregnant women prior to the labor period, unless in the judgment of the physician the potential benefits outweigh the possible hazards, because safe use in pregnancy prior to labor has not been established relative to possible adverse effects on fetal development.

When used as an obstetrical analgesic, meperidine crosses the placental barrier and can produce depression of respiration and psychophysiologic functions in the newborn. Resuscitation may be required [see OVERDOSAGE].

Meperidine appears in the milk of nursing mothers receiving the drug.

PRECAUTIONS

Do not use unless solution is clear and package is undamaged [see DOSAGE AND ADMINISTRATION].

General

Supraventricular Tachycardias

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

Convulsions

Meperidine may aggravate pre-existing convulsions in patients with convulsive disorders. If dosage is escalated substantially above recommended levels because of tolerance development, convulsions may occur in individuals without a history of convulsive disorders. The convulsive potential of meperidine may be further increased if prolonged infusions or repeated doses are administered due to high serum levels of normeperidine.

Acute Abdominal Conditions

The administration of meperidine or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special Risk Patients

Meperidine should be given with caution and the initial dose should be reduced in certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.
Information for Patients

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 provider if they are taking, or plan to take serotonergic medications [see WARNINGS, PRECAUTIONS; Drug Interactions].

Drug Interactions

Monoamine Oxidase Inhibitors

Meperidine is contraindicated in patients who are receiving monoamine oxidase (MAO) inhibitors or those who have recently received such agents [see CONTRAINDICATIONS]. Therapeutic doses of meperidine have occasionally precipitated unpredictable, severe, and occasionally fatal reactions in patients who have received such agents within 14 days [see WARNINGS]. 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 Injection in patients taking MAOIs or within 14 days of stopping such treatment.

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

Inhibitors of CYP3A4 and CYP2B6

The concomitant use of Meperidine Hydrochloride Injection and CYP3A4 inhibitors, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole), and protease inhibitors (e.g., ritonavir), or CYP2B6 can increase the plasma concentration of meperidine, resulting in increased or prolonged opioid effects. These effects could be more pronounced with concomitant use of Meperidine Hydrochloride Injection and CYP2B6 and CYP3A4 inhibitors, particularly when an inhibitor is added after a stable dose of Meperidine Hydrochloride Injection is achieved [see WARNINGS].

After stopping a CYP3A4 or CYP2B6 inhibitor, as the effects of the inhibitor decline, the meperidine plasma concentration will decrease [see CLINICAL PHARMACOLOGY], resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to oxycodone.

If concomitant use is necessary, consider dosage reduction of Meperidine Hydrochloride Injection until stable drug effects are achieved. Monitor patients for respiratory depression and sedation at frequent intervals.

If a CYP3A4 or CYP2B6 inhibitor is discontinued, consider increasing the Meperidine Hydrochloride Injection dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal.

Inducers of CYP3A4 or CYP2B6

The concomitant use of Meperidine Hydrochloride Injection and CYP3A4 or CYP2B6 inducers, such as rifampin, carbamazepine, and phenytoin, can decrease the plasma concentration of meperidine [see CLINICAL PHARMACOLOGY], resulting in decreased efficacy or onset of a withdrawal syndrome in
patients who have developed physical dependence to meperidine [see WARNINGS].

After stopping a CYP3A4 or CYP2B6 inducer, as the effects of the inducer decline, the meperidine plasma concentration will increase [see CLINICAL PHARMACOLOGY], which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression.

If concomitant use is necessary, consider increasing the Meperidine Hydrochloride Injection dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal. If a CYP3A4 or CYP2B6 inducer is discontinued, consider Meperidine Hydrochloride Injection dosage reduction and monitor for signs of respiratory depression.

Benzodiazepines and Other Central Nervous System (CNS) Depressants

Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants such as alcohol, other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, and other opioids, can increase the risk of respiratory depression, profound sedation, coma, and death.

Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation [see WARNINGS].

Serotonergic Drugs

The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system, such as selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that effect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), and monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue), has resulted in serotonin syndrome [see WARNINGS, PRECAUTIONS; Information for Patients].

If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue Meperidine Hydrochloride Injection if serotonin syndrome is suspected.

Carcinogenesis, Mutagenesis, Impairment of Fertility

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 CLINICAL PHARMACOLOGY, ADVERSE REACTIONS].

Pregnancy

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].

Labor or Delivery

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

Nursing Mothers

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

Pediatric Use

Meperidine Hydrochloride administered by the intravenous route via a compatible infusion device is not recommended for use in individuals younger than 19 years of age.

Geriatric Use

Elderly patients (aged 65 years or older) may have increased sensitivity to meperidine hydrochloride. In general, use caution when selecting a dosage for an elderly patient, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy. Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of Meperidine Hydrochloride Injection slowly in geriatric patients and monitor closely for signs of central nervous system and respiratory depression [see WARNINGS].

ADVERSE REACTIONS

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

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

Nervous System. Euphoria, dysphoria, weakness, headache, agitation, tremor, uncoordinated muscle movements, severe convulsions, transient hallucinations and disorientation, visual disturbances. Inadvertent injection about a nerve trunk may result in sensory-motor paralysis which is usually, though not always, transitory.

Gastrointestinal. Dry mouth, constipation, biliary tract spasm.

Cardiovascular. Flushing of the face, tachycardia, bradycardia, palpitation, hypotension (see WARNINGS), syncope, phlebitis following intravenous injection.
Genitourinary. Urinary retention.

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

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

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

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

Androgen deficiency. Cases of androgen deficiency have occurred with chronic use of opioids [see CLINICAL PHARMACOLOGY].

DRUG ABUSE AND DEPENDENCE

Controlled Substance

Meperidine Hydrochloride Injection contains meperidine, a Schedule II controlled substance.

Abuse

Meperidine Hydrochloride Injection contains meperidine, a substance with a high potential for abuse similar to other opioids including, fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, and tapentadol. Meperidine Hydrochloride Injection can be abused and is subject to misuse, addiction, and criminal diversion [see WARNINGS].

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 persons with substance use disorders. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing, or referral, repeated "loss" of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating health care 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. Health care 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 Injection, 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 Injection
Abuse of Meperidine Hydrochloride Injection poses a risk of overdose and death. The risk is increased with concurrent abuse of Meperidine Hydrochloride Injection with alcohol and other central nervous system depressants.

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

**Dependence**

Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dosage reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene), mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

Meperidine Hydrochloride Injection should not be abruptly discontinued [see DOSAGE AND ADMINISTRATION]. If Meperidine Hydrochloride Injection is abruptly discontinued in a physically dependent patient, a withdrawal syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, and heart rate.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs [see PRECAUTIONS; Pregnancy].

**OVERDOSAGE**

**Clinical Presentation**

Acute overdose with Meperidine Hydrochloride Injection 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. In severe overdose, particularly by the intravenous route, apnea, circulatory collapse, cardiac arrest, and death may occur.

**Treatment of Overdose**

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

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

Because the duration of opioid reversal is expected to be less than the duration of action of meperidine
in Meperidine Hydrochloride Injection, carefully monitor the patient until spontaneous respiration is reliably re-established. 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 of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be begun with care and by titration with smaller than usual doses of the antagonist.

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 Injection slowly in patients with hepatic impairment and monitor closely for signs of central nervous system and respiratory depression.

**DOSAGE AND ADMINISTRATION**

**Important Dosage and Administration Instructions**

Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals [see WARNINGS].

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].

Monitor patients closely for respiratory depression, especially within the first 24 to 72 hours of initiating therapy and following dosage increases with Oxycodone and Aspirin Tablets and adjust the dosage accordingly [see WARNINGS].

For use as a single-dose unit to provide analgesia via the intravenous route using a compatible Hospira infusion device. Each vial is intended for SINGLE DOSE ONLY. When the dosing requirement is complete, the unused portion should be discarded in an appropriate manner.

Do not autoclave.

Physicians should completely familiarize themselves with a compatible Hospira infusion device before deciding to administer meperidine hydrochloride injection via the infuser.

Parenteral drug products should be inspected visually for particulate matter and discoloration whenever solution and container permit prior to administration.

When administered intravenously, meperidine hydrochloride should be given very slowly. Rapid intravenous injection increases the incidence of adverse reactions; severe respiratory depression, apnea, hypotension, peripheral circulatory collapse and cardiac arrest have occurred. This drug should be administered intravenously only if a narcotic antagonist (i.e., naloxone) and the facilities for assisted or controlled respiration are immediately available. When meperidine hydrochloride is given parenterally, especially intravenously, the patient should be lying down.

**Incompatibility**

Meperidine hydrochloride is incompatible with soluble barbiturates, aminophylline, heparin, morphine sulfate, methicillin, phenytoin, sodium bicarbonate, iodide, sulfadiazine and sulfisoxazole.

**Initial Dosage**

Adults
The usual initial dose for adult administration via a compatible Hospira infusion device is 10 mg, with a range of 1 to 5 mg per incremental dose. The recommended Lockout Interval is 6 to 10 minutes. The minimum recommended Lockout Interval is 5 minutes.

The physician may adjust the dosage either upward or downward; or, increase or decrease the Lockout Interval, depending on patient response. For continuous infusion the usual adult dose is 15 to 35 mg per hour administered intravenously as required.

**Dosage Modifications in Patients**

Reduced dosage is indicated in the very young or very old, in patients with impaired renal or hepatic function and in patients receiving other central nervous system depressants, including phenothiazines and other tranquilizers. For surgical patients, dosage should be based on response of the patient, other premedication and concomitant medications, the anesthetic being used and the nature and duration of the operation.

**Titration and Maintenance of Therapy**

Individually titrate Meperidine Hydrochloride Injection to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving Meperidine Hydrochloride Injection 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]. Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration.

If the level of pain increases after dosage stabilization, attempt to identify the source of increased pain before increasing the Meperidine Hydrochloride Injection 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.

**Discontinuation of Meperidine Hydrochloride Injection**

When a patient who has been taking meperidine hydrochloride regularly and may be physically dependent no longer requires therapy with Meperidine Hydrochloride Injection, taper the dose gradually, by 25% to 50% every 2 to 4 days, while monitoring carefully for signs and symptoms of withdrawal. If the patient develops these signs or symptoms, raise the dose to the previous level and taper more slowly, either by increasing the interval between decreases, decreasing the amount of change in dose, or both. Do not abruptly discontinue Meperidine Hydrochloride Injection in a physically-dependent patient [see WARNINGS, DRUG ABUSE AND DEPENDENCE].

**HOW SUPPLIED**

Meperidine Hydrochloride Injection, USP 10 mg/mL is supplied in a 30 mL single-dose container, NDC 0409-6030-04.

This syringe is for insertion into a compatible infusion device only. Remove cover from male Luer and attached to PCA set. To load syringe injector assembly into infusion device, refer to operating manual of infusion device. See instructions on cart for syringe inspection and assembly.

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

LAB-0833-2.0

12/2016

Hospira, Inc., Lake Forest, IL 60045 USA
MEPERIDINE HYDROCHLORIDE
meperidine hydrochloride injection, solution

Product Information

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## Active Ingredient/Active Moiety

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## Labeler

- Hospira, Inc. (141588017)

## Establishment

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Revised: 7/2017