PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[N]Demerol
(Meperidine Hydrochloride Injection USP)

50 mg/mL, 75 mg/mL and 100 mg/mL

Sterile Solution

Narcotic Analgesic

Hospira Healthcare Corporation
17300 Trans-Canada Highway
Kirkland, Québec
H9J 2M5

Date of Revision:
April 26, 2018

Submission Control No: 212492

TABLE OF CONTENTS

PART I: HEALTH PROFESSIONAL INFORMATION 3
SUMMARY PRODUCT INFORMATION 3
INDICATIONS AND CLINICAL USE 3
CONTRAINDICATIONS 4
WARNINGS AND PRECAUTIONS 4
ADVERSE REACTIONS 12
DRUG INTERACTIONS 14
DOSAGE AND ADMINISTRATION 15
OVERDOSAGE 19
ACTION AND CLINICAL PHARMACOLOGY 20
STORAGE AND STABILITY 22
SPECIAL HANDLING INSTRUCTIONS 23
DOSAGE FORMS, COMPOSITION AND PACKAGING 23

PART II: SCIENTIFIC INFORMATION 24
PHARMACEUTICAL INFORMATION 24

PATIENT MEDICATION INFORMATION 25

[N]Demerol
(Meperidine Hydrochloride Injection USP)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Intramuscular Intravenous Subcutaneous	Sterile solution 50 mg/mL 75 mg/mL 100 mg/mL	50 mg/mL(ampule), 75 mg/mL(ampule) and 100 mg/mL (ampule): Hydrochloric acid, sodium hydroxide, water for injection 50 mg/mL (vial) and 100 mg/mL (vial): Hydrochloric acid, metacresol, sodium hydroxide, water for injection

INDICATIONS AND CLINICAL USE

Adults
Demerol is indicated for the relief of acute episodes of moderate to severe pain.

Demerol is not indicated as an as-needed (prn) analgesic.

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

Geriatrics (> 65 years of age)
In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, concomitant disease or other drug therapy.

Pediatrics (< 18 years of age)
In general, dose selection for children should be cautious, usually starting at a lower dosage, up to the adult dose.

CONTRAINDICATIONS

- Patients who are hypersensitive to the active substance meperidine or other opioid analgesics or to any ingredient in the formulation. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.
- In patients with known or suspected mechanical gastrointestinal obstruction (e.g., bowel obstruction or strictures) or any diseases/conditions that affect bowel transit (e.g., ileus of any type).
- Patients with suspected surgical abdomen (e.g., acute appendicitis or pancreatitis).
- Patients with mild pain that can be managed with other pain medications.
- Patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus.
- Patients with acute respiratory depression, elevated carbon dioxide levels in the blood and cor pulmonale.
- Patients with acute alcoholism, delirium tremens, and convulsive disorders.
- Patients with severe CNS depression, increased cerebrospinal or intracranial pressure, and head injury.
- Patients taking monoamine oxidase (MAO) inhibitors (or within 14 days of such therapy).

WARNINGS AND PRECAUTIONS

SERIOUS WARNINGS AND PRECAUTIONS

Limitations of Use

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the risks of overdose and death with immediate release opioid formulations, Demerol (meperidine hydrochloride injection) should only be used in patients for whom alternative treatment options (e.g., non-opioid analgesics) are ineffective, not tolerated, or would be otherwise inadequate to provide appropriate management of pain (see DOSAGE AND ADMINISTRATION).

Addiction, Abuse, and Misuse

Demerol poses risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Each patient's risk should be assessed prior to prescribing Demerol, and all patients should be monitored regularly for the development of these behaviours or conditions (see WARNINGS AND PRECAUTIONS, Abuse and Misuse). Demerol should be stored securely to avoid theft or misuse.

Life-threatening Respiratory Depression: OVERDOSE

Serious, life-threatening, or fatal respiratory depression may occur with use of Demerol. Infants exposed in-utero or through breast milk are at risk of life-threatening respiratory

SERIOUS WARNINGS AND PRECAUTIONS

depression upon delivery or when nursed. Patients should be monitored for respiratory depression, especially during initiation of Demerol or following a dose increase. Further, instruct patients of the hazards related to taking opioids including fatal overdose.

Accidental Exposure
Accidental exposure of even one dose of Demerol, especially by children, can result in a fatal overdose of meperidine (see DOSAGE AND ADMINISTRATION, Disposal, for instructions on proper disposal).

Neonatal Opioid Withdrawal Syndrome
Prolonged maternal use of Demerol during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening (see WARNINGS AND PRECAUTIONS, Neonatal Opioid Withdrawal Syndrome (NOWS)).

Interaction with Alcohol
Caution should be observed when administering meperidine to patients who have been or are taking alcohol. Demerol should be avoided as it may result in dangerous additive effects, causing serious injury or death (see WARNINGS AND PRECAUTIONS and 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 AND PRECAUTIONS, Neurologic and DRUG INTERACTIONS).

- **Reserve concomitant prescribing of Demerol 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.**

General
Demerol should be stored securely to avoid theft or misuse.

Demerol should only be prescribed by persons knowledgeable in the continuous administration of potent opioids, in the management of patients receiving potent opioids for the treatment of pain, and in the detection and management of respiratory depression, including the use of opioid antagonists.

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

severe respiratory depression, cyanosis, and hypotension, and have resembled the syndrome of acute opioid overdose. In other reactions the predominant manifestations have been hyperexcitability, convulsions, tachycardia, hyperpyrexia, and hypertension. Although it is not known that other narcotics are free of the risk of such reactions, virtually all of the reported reactions have occurred with meperidine. If an opioid is needed in such patients, a sensitivity test should be performed in which repeated, small, incremental doses of morphine are administered over the course of several hours while the patient's condition and vital signs are under careful observation. (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 safely of opioid antagonists in the treatment of these reactions is unknown.)

Patients should be cautioned not to consume alcohol while taking Demerol as it may increase the chance of experiencing serious adverse events, including death.

Demerol should not be used for the treatment of chronic pain. Demerol should only be used in the treatment of acute episodes of moderate to severe pain. Prolonged DEMEROL use may increase the risk of toxicity (e.g., seizures) from the accumulation of the meperidine metabolite, normeperidine.

Hyperalgesia that will not respond to a further dose increase of meperidine can occur at particularly high doses. A meperidine dose reduction or change in opioid may be required.

Abuse and Misuse

Like all opioids, Demerol is a potential drug of abuse and misuse, which can lead to overdose and death. Therefore, Demerol should be prescribed and handled with caution.

Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. All patients receiving opioids should be routinely monitored for signs of misuse and abuse.

Opioids, such as Demerol, should be used with particular care in patients with a history of alcohol and illicit/prescription drug abuse. However, concerns about abuse, addiction, and diversion should not prevent the proper management of pain.

Cardiovascular

Meperidine administration may result in severe hypotension in patients whose ability to maintain adequate blood pressure is compromised by reduced blood volume, or concurrent administration of drugs such as, other opioid analgesics, phenothiazines and other tranquilizers, sedative/hypnotics (including barbiturates), tricyclic antidepressants or general anesthetics, and other CNS depressants (including alcohol). These patients should be monitored for signs of hypotension after initiating or titrating the dose of Demerol.

The use of Demerol in patients with circulatory shock should be avoided as it may cause vasodilation that can further reduce cardiac output and blood pressure.

Rapid intravenous injection of opioid analgesics increases the possibility of hypotension and respiratory depression and should be avoided (see **DOSAGE AND ADMINISTRATION**).

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.

Dependence/Tolerance

As with other opioids, tolerance and physical dependence may develop upon repeated administration of Demerol and there is a potential for development of psychological dependence.

Physical dependence and tolerance reflect the neuroadaptation of the opioid receptors to chronic exposure to an opioid, and are separate and distinct from abuse and addiction. Tolerance, as well as physical dependence, may develop upon repeated administration of opioids, and are not by themselves evidence of an addictive disorder or abuse.

Patients on prolonged therapy should be tapered gradually from the drug if it is no longer required for pain control. Withdrawal symptoms may occur following abrupt discontinuation of therapy or upon administration of an opioid antagonist. Some of the symptoms that may be associated with abrupt withdrawal of an opioid analgesic include body aches, diarrhea, goosebumps, loss of appetite, nausea, nervousness or restlessness, anxiety, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning (see **ADVERSE REACTIONS; DOSAGE AND ADMINISTRATION, Adjustment or Reduction of Dosage**).

Use in Drug and Alcohol Addiction

Demerol is an opioid with no approved use in the management of addictive disorders. Its proper usage in individuals with drug or alcohol dependence, either active or in remission is for the management of pain requiring opioid analgesia. Patients with a history of addiction to drugs or alcohol may be at higher risk of becoming addicted to Demerol; extreme caution and awareness are warranted to mitigate the risk.

Endocrine

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.

Gastrointestinal Effects
Meperidine and other morphine-like opioids have been shown to decrease bowel motility. Meperidine may obscure the diagnosis or clinical course of patients with acute abdominal conditions (see **CONTRAINDICATIONS**).

Neonatal Opioid Withdrawal Syndrome (NOWS)
Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening.

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.

Demerol is not recommended to be used in pregnant women unless, in the judgement of the physician, the potential benefits outweigh the risks. If Demerol was used during pregnancy, special attention to NOWS is warranted.

Neurologic
Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol): Meperidine should be used with caution and in a reduced dosage during concomitant administration of other opioid analgesics, general anesthetics, phenothiazines and other tranquilizers, sedative-hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, benzodiazepines, centrally-active anti-emetics and other CNS depressants. Respiratory depression, hypotension and profound sedation, coma or death may result.

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**). 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 Demerol 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**).

Demerol should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects, including death (see **CONTRAINDICATIONS**; **ADVERSE REACTIONS, Sedation;** and **DRUG INTERACTIONS**).

Severe pain antagonizes the subjective and respiratory depressant actions of opioid analgesics. Should pain suddenly subside, these effects may rapidly become manifest.

Meperidine may aggravate preexisting 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.

Head Injury: The respiratory depressant effects of meperidine, and the capacity to elevate cerebrospinal fluid pressure, may be greatly increased in the presence of an already elevated intracranial pressure produced by trauma or other intracranial lesions. Also, meperidine may produce confusion, miosis, vomiting and other side effects which obscure the clinical course of patients with head injury. In such patients, meperidine must be used with extreme caution and only if it is judged essential (see **CONTRAINDICATIONS).**

Serotonin Syndrome: Demerol could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs (e.g. anti-depressants, migraine medications). Treatment with the serotoninergic drug should be discontinued if such events (characterized by clusters of symptoms such as hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma) occur and supportive symptomatic treatment should be initiated. Demerol should not be used in combination with MAO inhibitors or serotonin-precursors (such as L-tryptophan, oxitriptan) and should be used with caution in combination with other serotonergic drugs (triptans, certain tricyclic antidepressants, lithium, tramadol, St. John's Wort) due to the risk of serotonergic syndrome (see **DRUG INTERACTIONS**).

Peri-Operative Considerations

Demerol is not indicated for pre-emptive analgesia (administration pre-operatively for the management of post-operative pain).

In the case of planned chordotomy or other pain-relieving operations, patients should not be treated with Demerol for at least 24 hours before the operation and Demerol should not be used in the immediate post-operative period.

Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. Thereafter, if Demerol is to be continued after the patient recovers from the post-operative period, a new dosage should be administered in accordance with the changed need for pain relief. The risk of withdrawal in opioid-tolerant patients should be addressed as clinically indicated.

The administration of analgesics in the peri-operative period should be managed by healthcare providers with adequate training and experience (e.g., by an anesthesiologist).

Meperidine and other morphine-like opioids have been shown to decrease bowel motility. Ileus is a common post-operative complication, especially after intra-abdominal surgery with opioid analgesia. Caution should be taken to monitor for decreased bowel motility in post-operative patients receiving opioids. Standard supportive therapy should be implemented.

Demerol should not be used in the early post-operative period (12 to 24 hours post-surgery) unless the patient is ambulatory and gastrointestinal function is normal.

Psychomotor Impairment

Demerol may impair the mental and/or physical abilities needed for certain potentially hazardous activities such as driving a car or operating machinery. Patients should be cautioned accordingly. Patients should also be cautioned about the combined effects of meperidine with other CNS depressants, including other opioids, phenothiazine, sedative/hypnotics and alcohol.

Respiratory

Respiratory Depression: Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression from opioid use, 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. Meperidine should be used with extreme caution in patients with substantially decreased respiratory reserve, pre-existing respiratory depression, hypoxia or hypercapnia. Meperidine should generally be avoided in the presence of an acute asthmatic attack (see **CONTRAINDICATIONS)**.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of Demerol, the risk is greatest during the initiation of therapy or following a dose increase. Patients should be closely monitored for respiratory depression when initiating therapy with Demerol and following dose increases.

Life-threatening respiratory depression is more likely to occur in the elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients.

To reduce the risk of respiratory depression, proper dosing and titration of Demerol are essential. Overestimating the Demerol dose when converting patients from another opioid product can result in a fatal overdose with the first dose. In these patients, the use of non-opioid analgesics should be considered, if feasible (see **WARNINGS AND PRECAUTIONS**, **Special Populations**, **Special Risk Groups**; and **DOSAGE AND ADMINISTRATION**).

Use in Patients with Chronic Pulmonary Disease: Monitor patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression for respiratory depression, particularly when initiating therapy and titrating with Demerol, as in these patients,

even usual therapeutic doses of Demerol may decrease respiratory drive to the point of apnea. In these patients, use of alternative non-opioid analgesics should be considered, if possible. The use of Demerol is contraindicated in Patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus (see **CONTRAINDICATIONS**).

Sexual Function/Reproduction

Long-term use of opioids may be associated with decreased sex hormone levels and symptoms such as low libido, erectile dysfunction, or infertility (see **ADVERSE REACTIONS**, **Post-Marketing Experience**).

Special Populations

Special Risk Groups: Meperidine should be administered with caution to patients with a history of alcohol and drug abuse and in a reduced dosage to debilitated patients, and in patients with severely impaired hepatic, renal, or pulmonary function, Addison's disease, hypothyroidism, myxedema, toxic psychosis, prostatic hypertrophy or urethral stricture.

Pregnant Women: Studies in human have not been conducted. Demerol crosses the placental barrier and is not recommended to be administered to pregnant women unless, in the judgement of the physician, potential benefits outweigh the risks.

Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal Opioid Withdrawal Syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening (see **WARNINGS AND PRECAUTIONS, Neonatal Opioid Withdrawal Syndrome (NOWS)**).

Pregnant women using opioids should not discontinue their medication abruptly as this can cause pregnancy complication such as miscarriage or still-birth. Tapering should be slow and under medical supervision to avoid serious adverse events to the fetus.

Labour, Delivery and Nursing Women: Since opioids can cross the placental barrier and are excreted in breast milk, Demerol is not recommended to be used in nursing women and during labour and delivery unless, in the judgement of the physician, the potential benefits outweigh the risks. Life-threatening respiratory depression can occur in the infant if opioids are administered to the mother. Naloxone, a drug that counters the effects of opioids, should be readily available if Demerol is used in this population.

Geriatrics (> 65 years of age): In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range and titrate slowly, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see **DOSAGE AND ADMINISTRATION**).

Pediatrics (< 18 years of age): In general, dose selection for children should be cautious, usually starting at a lower dosage, up to the adult dose (see **DOSAGE AND ADMINISTRATION**).

Usage in Ambulatory Patients
Meperidine 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, like other opioids, may produce orthostatic hypotension in ambulatory patients.

Patients with Hepatic or Renal Impairment
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.

ADVERSE REACTIONS

Adverse Drug Reaction Overview
Adverse effects of Demerol (meperidine hydrochloride injection) are similar to those of other opioid analgesics, and represent an extension of pharmacological effects of the drug class. The major hazards of opioids include respiratory and central nervous system depression and to a lesser degree, circulatory depression, respiratory arrest, shock and cardiac arrest.

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

Sedation: Sedation is a common side effect of opioid analgesics, especially in opioid naïve individuals. Sedation may also occur partly because patients often recuperate from prolonged fatigue after the relief of persistent pain. Most patients develop tolerance to the sedative effects of opioids within three to five days and, if the sedation is not severe, will not require any treatment except reassurance. If excessive sedation persists beyond a few days, the dose of the opioid should be reduced and alternate causes investigated. Some of these are: concurrent CNS depressant medication, hepatic or renal dysfunction, brain metastases, hypercalcemia and respiratory failure. If it is necessary to reduce the dose, it can be carefully increased again after three or four days if it is obvious that the pain is not being well controlled. Dizziness and unsteadiness may be caused by postural hypotension, particularly in elderly or debilitated patients, and may be alleviated if the patient lies down.

Nausea and Vomiting: Nausea is a common side effect on initiation of therapy with opioid analgesics and is thought to occur by activation of the chemoreceptor trigger zone, stimulation of the vestibular apparatus and through delayed gastric emptying. The prevalence of nausea declines following continued treatment with opioid analgesics. When instituting therapy with an opioid for chronic pain, the routine prescription of an antiemetic should be considered. In the cancer patient, investigation of nausea should include such causes as constipation, bowel obstruction, uremia, hypercalcemia, hepatomegaly, tumor invasion of celiac plexus and concurrent use of drugs with emetogenic properties. Persistent nausea which does not respond to

dosage reduction may be caused by opioid-induced gastric stasis and may be accompanied by other symptoms including anorexia, early satiety, vomiting and abdominal fullness. These symptoms respond to chronic treatment with gastrointestinal prokinetic agents.

Constipation: Practically all patients become constipated while taking opioids on a persistent basis. In some patients, particularly the elderly or bedridden, fecal impaction may result. It is essential to caution the patients in this regard and to institute an appropriate regimen of bowel management at the start of prolonged opioid therapy. Stimulant laxatives, stool softeners, and other appropriate measures should be used as required. As fecal impaction may present as overflow diarrhea, the presence of constipation should be excluded in patients on opioid therapy prior to initiating treatment for diarrhea.

Other adverse reactions include:

Nervous System
Euphoria, dysphoria, weakness, headache, agitation, tremor, severe convulsions, uncoordinated muscle movements, 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 and Precautions**), 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.

Post-Marketing Experience
Androgen deficiency: 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. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.

DRUG INTERACTIONS

Overview

Interaction with Benzodiazepines and Other Central Nervous System (CNS) Depressants: Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants (e.g. other opioids, sedatives/hypnotics, antidepressants, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, phenothiazines, neuroleptics, antihistamines, antiemetics, and alcohol) and beta-blockers, increases 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 AND PRECAUTIONS, Neurologic, Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol) and Psychomotor Impairment**). Demerol should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects.

Drug-Drug Interactions

The concomitant use of other central nervous system depressants including sedatives or hypnotics (including barbiturates), other narcotic analgesics, tricyclic antidepressants, general anesthetics, phenothiazines, tranquilizers and alcohol may produce additive depressant effects. Respiratory depression, hypotension and profound sedation or coma may occur.

Coadministration of meperidine with a serotonergic agent, such as a Selective Serotonin Re-uptake Inhibitor or a Serotonin Norepinephrine Re-uptake Inhibitor, may increase the risk of serotonin syndrome, a potentially life-threatening condition (see **WARNINGS AND PRECAUTIONS**).

MAO (Monoamine Oxidose) Inhibitors

Meperidine, when given to a patient receiving a MAO inhibitor, may precipitate CNS excitation or depression. Some reactions are characterized by excitation, sweating, hypertension, tachycardia, hyperpyrexia and convulsions. Other reactions have included respiratory depression, cyanosis, fever, rigidity, hypotension, unconsciousness, nystagmus, deep coma, and have resembled the syndrome of acute narcotic overdose. Several deaths have been reported. If an opioid is needed in such patients, a sensitivity test should be performed in which repeated, small, incremental doses of morphine are administered over the course of several hours while the patient's condition and vital signs are under observation. (Intravenous hydrocortisone or prednisolone have been used to treat severe reactions, with the addition of intravenous chlorpro-mazine in those cases exhibiting hypertension and hyperpyrexia. The usefulness and safety of opioid antagonists in the treatment of these reactions is unknown.)

Skeletal Muscle Relaxants

Meperidine may enhance the neuromuscular-blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

Cimetidine/Ranitidine

Cimetidine reduced the clearance and volume of distribution of meperidine in healthy subjects, whereas ranitidine did not.

Drug-Lifestyle Interactions
The concomitant use of alcohol should be avoided (see **WARNINGS AND PRECAUTIONS, General**).

Incompatibility

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

DOSAGE AND ADMINISTRATION

Demerol should only be used in patients for whom alternative treatment options are ineffective or not tolerated (e.g., non-opioid analgesics).

For acute pain, it is recommended that Demerol be used for a maximum of 7 days at the lowest dose that provides adequate pain relief.

All doses of opioids carry an inherent risk of fatal or non-fatal adverse events. This risk is increased with higher doses. If Demerol is used for more than 7 days, it is recommended that the daily dose not exceed 110 mg (90 morphine milligram equivalent). Each patient should be assessed for their risk prior to prescribing Demerol, as the likelihood of experiencing serious adverse events can depend upon the type of opioid, duration of treatment, level of pain as well as the patient's own level of tolerance. In addition, the level of pain should be assessed routinely to confirm the most appropriate dose and the need for further use of Demerol (see DOSAGE &ADMINISTRATION - Adjustment or reduction of Dosage).

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

Intramuscular Injections
Meperidine should be injected well within the body of a large muscle.

Dosing Considerations
Demerol should be used with caution within 12 hours pre-operatively and within the first 12-24 hours post-operatively (see **WARNINGS AND PRECAUTIONS, Peri-operative Considerations**).

Demerol is not indicated for rectal administration

Recommended Dose and Dosage Adjustment

For relief of Pain:
Dosage should be adjusted according to the severity of the pain and the response of the patient. While subcutaneous administration is suitable for occasional use, intramuscular administration is preferred when repeated doses are required. If intravenous administration is required, dosage should be decreased and the injection made very slowly, preferably utilizing a diluted solution such as sodium chloride 0.45%, sodium chloride 0.9%, dextrose 5% in water and dextrose-saline combinations. Meperidine is less effective orally than on parenteral administration. The dose of Demerol (meperidine hydrochloride injection) should be proportionately reduced (usually by 25 to 50 per cent) when administered concomitantly with phenothiazines and many other tranquilizers since they potentiate the action of Demerol.

Adults
The usual dosage is 50 to 150 mg intramuscularly, subcutaneously, or orally, every 3 to 4 hours as necessary. If intravenous administration is decided upon, the dosage should be reduced to 25 to 50 mg.

Elderly
Dosage should be reduced.

Children
The usual dosage is 1.1 to 1.8 mg/kg intramuscularly or subcutaneously up to the adult dose, every 3 or 4 hours as necessary.

For Preoperative Medication:

Adults
The usual dosage is 50 to 100 mg intramuscularly or subcutaneously, 30 to 90 minutes before the beginning of anesthesia.

Elderly
Dosage should be reduced.

Children
The usual dosage is 1.1 mg/kg (0.5 mg/lb) to 2.2 mg/kg (1 mg/lb) intramuscularly or subcutaneously up to the adult dose, 30 to 90 minutes before the beginning of anesthesia.

For Support of Anesthesia
Repeated slow intravenous injections of fractional doses (e.g., 10 mg/mL) or continuous intravenous infusion of a more dilute solution (e.g., 1 mg/mL) should be used. The dose should be titrated to the needs of the patient and will depend on the premedication and type of anesthesia being employed, the characteristics of the particular patient, and the nature and duration of the operative procedure.

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

For the equivalences of commonly used opioid analgesics, please refer to **Table 1**.

Conversion ratios for opioids are subject to variations in kinetics governed by genetics and other factors. When switching from one opioid to another, consider reducing the calculated dose by 25-50% to minimize the risk of overdose. Subsequently, up-titrate the dose, as required, to reach the appropriate maintenance dose.

Table 1: OPIOID ANALGESICS: APPROXIMATE ANALGESIC EQUIVALENCES[1]

Drug	Equivalent Dose (mg)[2] (compared to morphine 10 mg IM)		Duration of Action (hours)
	Parenteral	**Oral**	
Strong Opioid Agonists:			
Morphine	10	60[3]	3-4
Oxycodone	15	30[4]	2-4
Hydromorphone	1.5	7.5	2-4
Anileridine	25	75	2-3
Levorphanol	2	4	4-8
Meperidine[6]	75	300	1-3
Oxymorphone	1.5	5 (rectal)	3-4
Methadone[5]	-	-	-
Heroin	5-8	10-15	3-4
Weak Opioid Agonists:			
Codeine	120	200	3-4
Propoxyphene	50	100	2-4
Mixed Agonist-Antagonists[7]:			
Pentazocine[6]	60	180	3-4
Nalbuphine	10	-	3-6
Butorphanol	2	-	3-4

Footnotes:

[1]References:

Expert Advisory Committee on the Management of Severe Chronic Pain in Cancer Patients, Health and Welfare Canada. Cancer pain: A monograph on the management of cancer pain. Ministry of Supplies and Services Canada, 1987. Cat. No. H42-2/5-1984E.

Foley KM. The treatment of cancer pain. N Engl J Med 1985;313(2):84-95.

Aronoff GM, Evans WO. Pharmacological management of chronic pain: A review. In: Aronoff GM, editor. Evaluation and treatment of chronic pain. 2nd ed. Baltimore (MD): Williams and Wilkins; 1992. p. 359-68.

Cherny NI, Portenoy RK. Practical issues in the management of cancer pain. In: Wall PD, Melzack R, editors. Textbook of pain. 3rd ed. New York: Churchill Livingstone; 1994. p. 1437-67.

[2] **Most of the data were derived from single-dose, acute pain studies and should be considered an approximation for selection of doses when treating chronic pain. As analgesic conversion factors are approximate and patient response may vary, dosing should be individualized according to relief of pain and side effects. Because of incomplete cross-tolerance, dose reductions of 25% to 50% of the equianalgesic dose may be appropriate in some patients when converting from one opioid to another, particularly at high doses.[†] Upward titration may be required to reach appropriate maintenance doses.**

[†]Levy MH. Pharmacologic treatment of cancer pain. N Engl J Med 1996;335:1124-1132.

[3] **For acute pain, the oral or rectal dose of morphine is six times the injectable dose. However, for chronic dosing, clinical experience indicates that this ratio is 2-3:1 (i.e., 20-30 mg of oral or rectal morphine is equivalent to 10 mg of parenteral morphine).**

[4] Based on single entity oral oxycodone in acute pain.

[5] Extremely variable equianalgesic dose. Patients should undergo individualized titration starting at an equivalent to 1/10 of the morphine dose.

[6] Not recommended for the management of chronic pain.

[7] Mixed agonist-antagonists can precipitate withdrawal in patients on pure opioid agonists.

Geriatrics:

Respiratory depression has occurred in the elderly following administration of large initial doses of opioids to patients who were not opioid-tolerant or when opioids were co-administered with

other agents that can depress respiration. Demerol should be initiated at a low dose and slowly titrated to effect (see **WARNINGS AND PRECAUTIONS**).

Use with Non-Opioid Medications:
If a non-opioid analgesic is being provided, it may be continued. If the non-opioid is discontinued, consideration should be given to increasing the opioid dose to compensate for the non-opioid analgesic. Demerol can be safely used concomitantly with usual doses of other non-opioid analgesics.

Dose Titration:
Dose titration is the key to success with opioid analgesic therapy. **Proper optimization of doses scaled to the relief of the individual's pain should aim at administration of the lowest dose which will achieve the overall treatment goal of satisfactory pain relief with acceptable side effects.**

Dosage adjustments should be based on the patient's clinical response.

Adjustment or Reduction of Dosage:

Physical dependence with or without psychological dependence tends to occur with chronic administration of opioids, including Demerol. Withdrawal (abstinence) symptoms may occur following abrupt discontinuation of therapy. These symptoms may include body aches, diarrhea, goosebumps, loss of appetite, nausea, nervousness or restlessness, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning.

Following successful relief of moderate to severe pain, periodic attempts to reduce the opioid dose should be made. Smaller doses or complete discontinuation may become feasible due to a change in the patient's condition or mental state. Patients on prolonged therapy should be withdrawn gradually from the drug if it is no longer required for pain control. In patients who are appropriately treated with opioid analgesics and who undergo gradual withdrawal for the drug, these symptoms are usually mild (see **WARNINGS AND PRECAUTIONS**). Tapering should be individualised and carried out under medical supervision.

Patient should be informed that reducing and/or discontinuing opioids decreases their tolerance to these drugs. If treatment needs to be re-initiated, the patient must start at the lowest dose and titrate up to avoid overdose.

Disposal
Demerol should be kept in a safe place, out of the sight and reach of children before, during and after use. Demerol should not be used in front of children, since they may copy these actions.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Symptoms: In chronic overdosage, which may occur in patients or addicts who are tolerant to its depressant effects, meperidine may produce tremors, muscle twitches, dilated pupils, hyperactive reflexes and convulsions. These excitatory symptoms are due to the accumulation of normeperidine.

Acute overdosage is likely to lead to respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin and sometimes bradycardia and hypotension. In severe overdosage, particularly by the intravenous route, apnea, circulatory collapse, cardiac arrest and death may occur.

Treatment: Primary attention should be given to re-establishing adequate respiratory exchange through appropriate attention to airway and provision of assisted or controlled ventilation. Intensive supportive therapy may also be required to correct shock. The specific antagonist naloxone hydrochloride can very rapidly counteract the severe respiratory depression and coma which may result from overdosage or unusual sensitivity to meperidine. If clinically significant respiratory or cardiovascular depression is present, an appropriate dose of naloxone hydrochloride should be administered, preferably intravenously. Patients should be closely observed to determine any need for further treatment with naloxone since its duration of action may be exceeded by that of meperidine, particularly if the dose of meperidine the patient received was large.

It should be noted that in subjects physically dependent on opioids, the administration of an opioid antagonist is likely to precipitate an acute withdrawal syndrome. The use of an opioid antagonist in such individuals should be avoided if possible, but if its use proves necessary, extreme caution should be observed. The initial dose should be reduced to 1/5 to 1/10 of that which would be indicated in a normal subject.

Where overdosage of meperidine is the result of oral ingestion, consideration should also be given to evacuating the stomach by emesis or gastric lavage.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Meperidine is an opioid analgesic which acts predominantly as a mu-agonist. In its effects on the central nervous system, meperidine resembles but is not identical to morphine.

Pharmacodynamics

Central Nervous System:
Meperidine produces respiratory depression by direct action on brain stem respiratory centres. The respiratory depression involves both a reduction in the responsiveness of the brain stem centres to increases in CO_2 tension and to electrical stimulation.

Meperidine depresses the cough reflex by direct effect on the cough centre in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

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 origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in the setting of meperidine overdose.

Onset of analgesic effect is faster (within 10 minutes) after subcutaneous or intramuscular administration, reaching a peak within about 1 hour that corresponds closely to the peak concentrations in plasma. In clinical use, the duration of effective analgesia is about 3 to 5 hours. Given parenterally, 75 to 100 mg of meperidine is approximately equivalent to 10 mg of morphine in analgesic effectiveness. At equi-analgesic dosage, the two agents are comparable in the degree of sedation and of respiratory depression they produce. Given parenterally, meperidine is more than twice as effective as given orally in terms of the total analgesic response obtained. This is consistent with an oral bioavailability of about 40 to 60%.

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 gastric, biliary and pancreatic secretions, spasm of the sphincter of Oddi, and transient elevations in serum amylase.

The effects of meperidine on smooth muscle are qualitatively similar, but in relation to analgesic effect less intense than those of other opioids. Meperidine does not cause as much constipation when given over prolonged periods of time. This may be related to its greater facility to enter the CNS, thereby producing analgesia at lower peripheral concentrations. At equi-analgesic dosage, the rise in pressure in the common bile duct induced by meperidine is less than that by morphine, but greater than that by codeine. Clinical doses of meperidine nevertheless slow gastric emptying sufficiently to delay absorption of other drugs significantly. The uterus of non-pregnant women is usually mildly stimulated by meperidine. Therapeutic doses given during active labor do not delay the birth process; in fact, the frequency, duration and amplitude of uterine contractions may sometimes be increased. Meperidine does not interfere with normal postpartum contraction or involution of the uterus and does not increase the incidence of postpartum hemorrhage.

Cardiovascular System:
Meperidine may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilatation may include pruritus, flushing, red eyes, hyperhidrosis and/or orthostatic hypotension.

In its effects on the cardiovascular system, meperidine generally resembles morphine, including its ability to release histamine upon parenteral administration. Heart rate is unlikely to be significantly affected with intramuscular administration but may increase, with intravenous

administration. As with morphine, respiratory depression leads to an accumulation of carbon dioxide which in turn produces cerebrovascular dilatation, increase in cerebral blood flow and elevation of cerebrospinal fluid pressure.

Endocrine System:
Opioids may influence the hypothalamic-pituitary-adrenal or -gonadal axes. Some changes that can be seen include an increase in serum prolactin, and decreases in plasma cortisol and testosterone. Clinical signs and symptoms may be manifest from these hormonal changes.

Immune System:
In vitro and animal studies indicate that opioids have a variety of effects on immune functions, depending on the context in which they are used. The clinical significance of these findings is unknown.

Pharmacokinetics

Following intramuscular injection, peak plasma concentration is usually obtained at about 45 minutes, but the range in time is wide. After oral administration, only about 50% of meperidine escapes first-pass metabolism. Peak concentrations in the plasma are usually observed in 1 to 2 hours. Approximately 60% is bound to plasma proteins. Meperidine is metabolized chiefly in the liver. The plasma elimination half-life is normally 3 to 4 hours, but this may be extended considerably in the presence of significant hepatic disease. In patients with cirrhosis, bioavailability may be increased as much as 80%. Meperidine is hydrolyzed to meperidinic acid, which in turn is partially conjugated. Meperidine also undergoes N-demethylation to normeperidine, which may then be hydrolyzed to normeperidinic acid and subsequently conjugated. Normeperidine has a considerably longer plasma elimination half life (15-20 hours) than its parent molecu1e. In the presence of renal insufficiency, normeperidine elimination is reduced.

At the usual values of urinary pH, or if the urine is alkaline, excretion of unchanged meperidine is negligible; urinary excretion of meperidine and normeperidine is enhanced by acidification of the urine. Meperidine crosses the placenta and appears in milk.

Special Populations and Conditions

Pediatrics (< 18 years of age): In general, dose selection for children should be cautious, usually starting at a lower dosage, up to the adult dose.

STORAGE AND STABILITY

Store between 20°C and 25°C. Protect from freezing.

SPECIAL HANDLING INSTRUCTIONS

Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Demerol is a sterile, nonpyrogenic, hypotonic solution.

Composition:
Each mL ampule contains 50 mg, 75 mg or 100 mg meperidine hydrochloride, sodium hydroxide and hydrochloric acid in water for injection.

Each mL solution in vial contains 50 mg or 100 mg meperidine hydrochloride, sodium hydroxide, metacresol and hydrochloric acid in water for injection.

Packaging:
50 mg/mL is supplied in 30 mL glass vials or ampules of 1 mL.
75 mg/mL is supplied in ampules of 1 mL.
100 mg/mL is supplied in 20 mL glass vials or ampules of 1mL.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

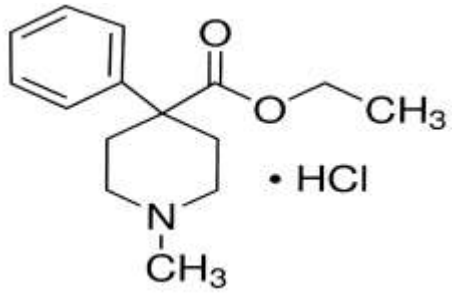
Drug Substance

Proper name:
Meperidine Hydrochloride

Chemical name:
Ethyl 1-methyl-4-phenylisonipecotate hydrochloride

Molecular formula and molecular mass:
Molecular formula: $C_{15}H_{21}NO_2 \cdot HCl$
Molecular mass: 283.79 g/moL

Structural formula:



Physicochemical Properties:
A white crystalline substance with a melting point of 186° to 189°C. It is readily soluble in water, has a neutral reaction and a slightly bitter taste. The solution is not decomposed by a short period of boiling.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

[N]Demerol
(Meperidine Hydrochloride Injection USP)

Read this carefully before you start taking Demerol. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about Demerol.

Serious Warnings and Precautions

- **Even if you take Demerol as prescribed you are at a risk for opioid addiction, abuse and misuse. This can lead to overdose and death.**
- **You may get life-threatening breathing problems while taking Demerol. This is less likely to happen if you take it as prescribed by your doctor. Babies are at risk of life-threatening breathing problems if their mothers take opioids while pregnant or nursing.**
- **If a person has not been prescribed Demerol, taking even one dose can cause a fatal overdose. This is especially true for children.**
- **If you took Demerol while you were pregnant, whether for short or long periods of time or in small or large doses, your baby can suffer life-threatening withdrawal symptoms after birth. This can occur in the days after birth and for up to 4 weeks after delivery. If your baby has any of the following symptoms:**
  - **has changes in their breathing (such as weak, difficult or fast breathing)**
  - **is unusually difficult to comfort**
  - **has tremors (shakiness)**
  - **has increased stools, sneezing, yawning, vomiting, or fever**

  Seek immediate medical help for your baby.
- **Taking Demerol 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.**

What is Demerol used for?

Demerol is an injection containing meperidine (an opioid analgesic) used to control your pain.

How does Demerol work?

Demerol is a painkiller belonging to the class of drugs known as opioids. It relieves pain by acting on specific nerve cells of the spinal cord and brain.
Demerol is used to treat severe pain in patients who need an opioid administered by injection. This is given under the skin, into the muscle or vein in doses or concentrations that are higher than those usually needed.

What are the ingredients in Demerol?

Medicinal ingredients: Meperidine Hydrochloride
Non-medicinal ingredients: 50 mg/mL(ampule), 75 mg/mL(ampule) and 100 mg/mL (ampule):
Hydrochloric acid, sodium hydroxide, water for injection
50 mg/mL (vial) and 100 mg/mL (vial):
Hydrochloric acid, metacresol, sodium hydroxide, water for injection

Demerol comes in the following dosage forms:
Sterile solution for injection, 50 mg/mL, 75 mg/mL and 100 mg/mL

Do not use Demerol if:

- your doctor did not prescribe it for you
- you are allergic to meperidine or any of the other ingredients in Demerol
- you can control your pain by the occasional use of other pain medications. This includes those available without a prescription
- you have severe asthma, trouble breathing, or other breathing problems
- you have any heart problems
- you have bowel blockage or narrowing of the stomach or intestines
- you have severe pain in your abdomen
- you have a head injury
- you are at risk for seizures
- you suffer from alcoholism
- you are taking or have taken within the past 2 weeks a Monoamine Oxidase inhibitor (MAOi) (such as phenelzine sulphate, tranylcypromine sulphate, moclobemide or selegiline)
- you are going to have, or recently had, a planned surgery

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Demerol. Talk about any health conditions or problems you may have, including if you:

- have a history of illicit or prescription drug or alcohol abuse
- have severe kidney, liver or lung disease

- have heart disease
- have low blood pressure
- have past or current depression
- suffer from chronic or severe constipation
- have problems with your thyroid, adrenal or prostate gland
- have, or had in the past hallucinations or other severe mental problems
- suffer from migraines
- are planning to become pregnant

Other warnings you should know about:

Opioid dependence and addiction: There are important differences between physical dependence and addiction. It is important that you talk to your doctor if you have questions or concerns about abuse, addiction or physical dependence.

Pregnancy, nursing, labour and delivery: Opioids can be transferred to your baby through breast milk, or while still in the womb. Demerol can then cause life-threatening breathing problems in your unborn baby or nursing infant. Your doctor will determine if the benefits of using Demerol outweigh the risks to your unborn baby or nursing infant.

If you are pregnant and are taking Demerol, it is important that you don't stop taking your medication all of a sudden. If you do, it can cause a miscarriage or a still-birth. Your doctor will monitor and guide you on how to slowly stop taking Demerol. This may help avoid serious harm to your unborn baby.

Driving and using machines: Before you do tasks which may require special attention, you should wait until you know how you react to Demerol. Demerol can cause:

- drowsiness
- dizziness or
- lightheadedness

This can usually occur after you take your first dose and when your dose is increased.

Disorder of the adrenal gland: You may develop a disorder of the adrenal gland called adrenal insufficiency. This means that your adrenal gland is not making enough of certain hormones. You may experience symptoms such as:

- nausea, vomiting
- feeling tired, weak or dizzy
- decreased appetite

You may be more likely to have problems with your adrenal gland if you have been taking opioids for longer than one month. Your doctor may do tests, give you another medication, and slowly take you off Demerol.

Serotonin Syndrome: Demerol can cause Serotonin Syndrome, a rare but potentially life-threatening condition. It can cause serious changes in how your brain, muscles and digestive

system work. You may develop Serotonin Syndrome if you take Demerol with certain anti-depressants or migraine medications.

Serotonin Syndrome symptoms include:

- fever, sweating, shivering, diarrhea, nausea, vomiting;
- muscle shakes, jerks, twitches or stiffness, overactive reflexes, loss of coordination;
- fast heartbeat, changes in blood pressure;
- confusion, agitation, restlessness, hallucinations, mood changes, unconsciousness, and coma.

Sexual Function/Reproduction: Long term use of opioids may lead to a decrease in sex hormone levels. It may also lead to low libido (desire to have sex), erectile dysfunction or being infertile.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Demerol:

- Alcohol. This includes prescription and non-prescription medications that contain alcohol. **Do not** drink alcohol while you are taking Demerol. It can lead to:
    - drowsiness
    - unusually slow or weak breathing
    - serious side effects or
    - a fatal overdose
- other sedative drugs which may enhance the drowsiness caused by Demerol
- other opioid analgesics (drugs used to treat pain)
- general anesthetics (drugs used during surgery)
- benzodiazepines (drugs used to help you sleep or that help reduce anxiety)
- antidepressants (for depression and mood disorders). **Do not** take Demerol with MAO inhibitors (MAOi) or if you have taken MAOi's in the last 14 days.
- drugs used to treat serious mental or emotional disorders (such as schizophrenia)
- antihistamines (drugs used to treat allergies)
- anti-emetics (drugs used for the prevention of vomiting)
- drugs used to treat muscle spasms and back pain
- drugs used to treat migraines (e.g. triptans)
- St. John's Wort

How to take Demerol:

For relief of pain
Adults
Your doctor will prescribe the lowest dose that works to control your pain. It is recommended that you only take Demerol for up to 7 days. If you need to take Demerol for longer, your doctor will determine the best dose for you to lower the risk of side effects and overdose. Higher doses can lead to more side effects and a greater chance of overdose.

The usual dosage is 50 to 150 mg intramuscularly or subcutaneously every 3 to 4 hours as necessary. If intravenous administration is decided upon, the dosage should be reduced to 25 to 50 mg.

Elderly
Dosage should be reduced.

Children
The usual dosage is 1.1 to 1.8 mg/kg intramuscularly or subcutaneously up to the adult dose, every 3 or 4 hours as necessary.

For Preoperative Medication
Adults
The usual dosage is 50 to 100 mg intramuscularly or subcutaneously, 30 to 90 minutes before the beginning of anesthesia.

Elderly
Dosage should be reduced.

Children
The usual dosage is 1.1 mg/kg (0.5 mg/lb) to 2.2 mg/kg (1 mg/lb) intramuscularly or subcutaneously up to the adult dose, 30 to 90 minutes before the beginning of anesthesia.

For Support of Anesthesia
Repeated slow intravenous injections of fractional doses (e.g., 10 mg/mL) or continuous intravenous infusion of a more dilute solution (e.g., 1 mg/mL) should be used. The dose should be titrated to the needs of the patient and will depend on the premedication and type of anesthesia being employed, the characteristics of the particular patient, and the nature and duration of the operative procedure.

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

Usual Starting Dose:

Your dose is tailored/personalized just for you.

Review your pain regularly with your doctor to determine if you still need Demerol. Be sure to use Demerol only for the condition for which it was prescribed.

If your pain increases or you develop any side effect as a result of taking Demerol, tell your doctor immediately.

Stopping your Medication

If you have been taking Demerol for more than a few days you should not stop taking it all of a sudden. Your doctor will monitor and guide you on how to slowly stop taking Demerol. You should do it slowly to avoid uncomfortable symptoms such as having:

- body aches
- diarrhea
- goosebumps
- loss of appetite
- nausea
- feeling nervous or restless
- runny nose
- sneezing
- tremors or shivering
- stomach cramps
- rapid heart rate (tachycardia)
- having trouble sleeping
- an unusual increase in sweating
- heart palpitations
- an unexplained fever
- weakness
- yawning

By reducing or stopping your opioid treatment, your body will become less used to opioids. If you start treatment again, you will need to start at the lowest dose. You may overdose if you restart at the last dose you took before you slowly stopped taking Demerol.

Refilling your Prescription for Demerol:

A new written prescription is required from your doctor each time you need more Demerol.

Only obtain prescriptions for this medicine from the doctor in charge of your treatment. Do not seek prescriptions from other doctors unless you switch to another doctor for your pain management.

Overdose:

If you think you have taken too much Demerol, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Signs of overdose may include:

- unusually slow or weak breathing
- dizziness
- confusion
- extreme drowsiness

What are possible side effects from using Demerol?

These are not all the possible side effects you may feel when taking Demerol. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- Drowsiness
- Insomnia
- Dizziness
- Fainting
- Nausea, vomiting, or a poor appetite
- Dry mouth
- Headache
- Problems with vision
- Weakness, uncoordinated muscle movement
- Itching
- Sweating
- Constipation
- Low sex drive, impotence (erectile dysfunction), infertility

Talk with your doctor or pharmacist about ways to prevent constipation when you start using Demerol.

Serious side effects and what to do about them				
Symptom / effect		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
RARE	**Overdose:** hallucinations, confusion, inability to walk normally, slow or weak breathing, extreme sleepiness, sedation, or dizziness, floppy muscles/low muscle tone, cold and clammy skin.			✓
	Respiratory Depression: slow, shallow or weak breathing.			✓
	Allergic Reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			✓
	Bowel Blockage (impaction): abdominal pain, severe constipation, nausea			✓
	Withdrawal: nausea, vomiting, diarrhea, anxiety, shivering, cold and clammy skin, body aches, loss of appetite, sweating.		✓	
	Fast, Slow or Irregular Heartbeat: heart palpitations.		✓	
	Low Blood Pressure: dizziness, fainting, light-headedness.	✓		
	Serotonin Syndrome: agitation or restlessness, loss of muscle control or muscle twitching, tremor, diarrhea			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
We encourage you to report serious or unexpected side effects to Health Canada. The information is used to check for new safety concerns about health products. As a consumer, your report contributes to the safe use of health products for everyone.

3 ways to report:

- Online at MedEffect: https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html;
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 1908C
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html).

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

Storage:

- **Keep unused or expired Demerol in a secure place to prevent theft, misuse or accidental exposure.**
- Store between 20°C and 25°C. Protect from freezing.
- **Keep Demerol under lock, out of sight and reach of children and pets.**
- **Never take medicine in front of small children as they will want to copy you. Accidental ingestion by a child is dangerous and may result in death. If a child accidentally takes Demerol, get emergency help right away.**

If you want more information about Demerol:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this consumer medication information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); or by calling 1-800-463-6001.

This leaflet was prepared by:

Hospira Healthcare Corporation
Kirkland, Québec H9J 2M5

Last Revised: April 26, 2018