

PRESCRIBING INFORMATION
INCLUDING PATIENT MEDICATION INFORMATION

[®]**DEMEROL**[®]

(meperidine hydrochloride)

tablets 50 mg

Opioid Analgesic

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®**DEMEROL**®

(meperidine hydrochloride)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Tablets, 50 mg	Calcium phosphate (dibasic), calcium sulfate, corn starch, stearic acid and talc. Gluten-, lactose-, sucrose- and tartrazine-free. <i>For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section.</i>

INDICATIONS AND CLINICAL USE

Adults

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

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 (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Geriatrics**).

Pediatrics (< 18 years of age)

The safety and efficacy of DEMEROL has not been studied in the pediatric population. Therefore the use of DEMEROL is not recommended in patients under 18 years of age.

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

- Patients with mild pain that can be managed with other pain medications.
- Patients with acute or severe bronchial asthma, chronic obstructive airway, status asthmaticus, substantially decreased respiratory reserve; hypoxia, elevated carbon dioxide levels in the blood, cor pulmonale and other preexisting respiratory depression. In such patients, even usual therapeutic doses of opioids may decrease respiratory drive while simultaneously increasing airway resistance to the point of apnea.
- Patients with acute alcoholism, delirium tremens, and convulsive disorders.
- Patients with severe CNS depression, increased cerebrospinal or intracranial pressure, and head injury. The respiratory depressant effects of DEMEROL 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.
- Patients taking monoamine oxidase (MAO) inhibitors (or within 14 days of such therapy). Therapeutic doses of DEMEROL have occasionally precipitated severe, unpredictable, and sometimes fatal reactions in patients who have received MAOIs within the previous 14 days. The mechanism of these reactions is unclear, but may be related to a pre-existing hyperphenylalaninemia. Some cases have been characterized by coma, severe respiratory depression, cyanosis and hypotension, and have resembled acute opioid overdose. Other cases have resembled serotonin toxicity; predominant manifestations have included hyperexcitability, agitation, convulsions, diarrhea, tachycardia, sweating, tremor, impaired consciousness, hyperpyrexia and hypertension (see also **DRUG INTERACTIONS**).

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 tablets) 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). DEMEROL should be stored securely to avoid theft or misuse.

SERIOUS WARNINGS AND PRECAUTIONS

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 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.

DEMEROL must be swallowed whole. Cutting, breaking, crushing, chewing, or dissolving DEMEROL can lead to dangerous adverse events including death (see WARNINGS AND PRECAUTIONS).

Accidental Exposure

Accidental ingestion of even one dose of DEMEROL, especially by children, can result in a fatal overdose of meperidine hydrochloride (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).

Interaction with Alcohol

The co-ingestion of alcohol with 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 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 closely for signs and symptoms of sedation and respiratory depression.

General

Patients should be instructed not to give DEMEROL (meperidine hydrochloride) tablets to anyone other than the patient for whom it was prescribed, as such inappropriate use may

have severe medical consequences, including death. 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.

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 hydrochloride can occur at particularly high doses. A meperidine hydrochloride 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.

DEMEROL is intended for oral use only. The tablets should be swallowed whole, and not chewed or crushed. Abuse of oral dosage forms can be expected to result in serious adverse events, including death.

Cardiovascular

Meperidine hydrochloride administration may result in severe hypotension in postoperative patients or in patients whose ability to maintain adequate blood pressure is compromised by reduced blood volume, or concurrent administration of drugs such as phenothiazines and other tranquilizers, sedative/hypnotics, tricyclic antidepressants or general anesthetics. 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.

Supraventricular Tachycardias: DEMEROL 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.

DEMEROL, like other narcotics, may produce orthostatic hypotension in ambulatory patients.

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.

Like other narcotics, DEMEROL is subject to the provisions of the Narcotic Control Act.

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

Neonatal Opioid Withdrawal Syndrome (NOWS)

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

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.

Neurologic

Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol): Meperidine hydrochloride 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. Sedation, respiratory depression, hypotension, 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 sedation and respiratory depression.

Advise both patients and caregivers about the risks of sedation and respiratory depression 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.

Convulsions: DEMEROL 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. All opioids may induce or aggravate seizures in some clinical settings.

Head Injury: The respiratory depressant effects of meperidine hydrochloride, and the capacity to elevate cerebrospinal fluid pressure, may be greatly increased in the presence of an already elevated intracranial pressure produced by trauma. Also, meperidine hydrochloride may produce confusion, miosis, vomiting and other side effects which obscure the clinical course of patients with head injury. In such patients, meperidine hydrochloride 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 serotonergic 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**).

DEMEROL should not be used in combination with serotonergic products due to the risk of serotonin toxicity (see **CONTRAINDICATIONS** and **DRUG INTERACTIONS, Drug-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 hydrochloride 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 hydrochloride 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 hydrochloride

should be used with extreme caution in patients with substantially decreased respiratory reserve, pre-existing respiratory depression, hypoxia or hypercapnia (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 hydrochloride 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 pulmonary, hepatic or renal function, Addison's disease, hypothyroidism, myxedema, toxic psychosis, prostatic hypertrophy or urethral stricture (due to the risk of urinary retention), sickle cell anemia, delirium tremens, kyphoscoliosis associated with respiratory depression, pheochromocytoma. In patient with pheochromocytoma, DEMEROL has been reported to provoke hypertension. Meperidine should also be used with cautions in patients with decreased level of consciousness.

Pregnant Women: Studies in humans have not been conducted. DEMEROL crosses the placental barrier and is not recommended to be administered to pregnant women unless, in the

judgment 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, ADVERSE REACTIONS**).

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.

DEMEROL should not be used in pregnant women prior to the labor period, unless 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.

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 judgment 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; resuscitation may be required. Naloxone, a drug that counters the effects of opioids, should be readily available if DEMEROL is used in this population.

Pediatrics (< 18 years of age): The safety and efficacy of DEMEROL have not been studied in the pediatric population. Therefore, use of DEMEROL is not recommended in patients under 18 years of age.

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** and **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Geriatrics**).

Patients with Hepatic Impairment:

DEMEROL should be given with caution and the initial dose should be reduced in patients with severe impairment of hepatic function (see **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Geriatrics**).

Patients with Renal Impairment:

DEMEROL should be given with caution and the initial dose should be reduced in patients such with severe impairment of renal function (see **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Geriatrics**).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse effects of DEMEROL (meperidine hydrochloride) tablets 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 effects of DEMEROL are 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:

Cardiovascular: flushing of the face, tachycardia, bradycardia, palpitation, hypotension (see **WARNINGS AND PRECAUTIONS**), syncope.

Dermatologic/Allergic: pruritus, urticaria, other skin rashes; Hypersensitivity reactions: anaphylaxis including shock.

Gastrointestinal: dry mouth, constipation, biliary tract spasm.

General and CNS: mood changes (such as euphoria, dysphoria), weakness, headache, agitation, tremor, muscle twitches, severe convulsions, uncoordinated muscle movements, transient hallucinations and disorientation, delirium or confusion, visual disturbances.

Genitourinary: urinary retention.

Other: Antidiuretic effect.

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.

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.

Cardiac disorders: myocardial infarction (in the context of Kounis syndrome).

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, tricyclic antidepressants, tranquilizers, general anesthetics, antipsychotics, phenothiazines, antihistamines, antiemetics, and alcohol) and beta-blockers, increases the risk of sedation, respiratory depression, 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 sedation and respiratory depression (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

Acyclovir: Plasma concentrations of meperidine and its metabolite, normeperidine, may be increased by acyclovir, thus caution should be used with concomitant administration.

Cimetidine: Cimetidine reduced the clearance and volume of distribution of DEMEROL and also the formation of the metabolite normeperidine; thus caution should be used with concomitant administration.

MAO inhibitors: DEMEROL is contraindicated in patients who are receiving MAO inhibitors or those who have recently received such agents (i.e phenelzine, linezolid, selegiline, rasagiline) (see **CONTRAINDICATIONS**).

Morphine agonist-antagonists: Use of DEMEROL with morphine agonist-antagonists (buprenorphine, nalbuphine, pentazocine) may result in decreased analgesic effect and withdrawal syndrome due to competitive blocking of receptors.

Phenytoin: The hepatic metabolism of DEMEROL may be enhanced by phenytoin. Concomitant administration may result in reduced half-life and bioavailability of DEMEROL, and an increase in normeperidine concentration; thus caution should be exercised when used concomitantly.

Ritonavir: Plasma concentrations of the metabolite normeperidine may be increased by ritonavir, thus caution should be exercised when used concomitantly.

Serotonergic products: Cases of serotonin syndrome have been reported in patients taking DEMEROL concomitantly with serotonergic drugs such as selective serotonin reuptake inhibitors (SSRIs), serotonin non selective reuptake inhibitors (SNRIs), and with St. John's wort (*Hypericum perforatum*) (see **WARNINGS AND PRECAUTIONS, Neurologic**).

Skeletal muscle relaxants: Opioid analgesics, including meperidine, may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increase degree of respiratory depression.

Drug-Lifestyle Interactions

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

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).

DEMEROL must be swallowed whole. Cutting, breaking, crushing, chewing, or dissolving DEMEROL can lead to dangerous adverse events including death (see WARNINGS AND PRECAUTIONS).

Dosing Considerations

DEMEROL (meperidine hydrochloride) 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.

DEMEROL may be taken with or without food, with a glass of water.

DEMEROL should be used only for two days or less, for the relief of acute pain. The total daily dose should not exceed 600 mg.

Dosage should be adjusted according to the severity of the pain and the response of the patient. The dose of DEMEROL should be proportionally reduced (usually by 25 to 50%) when administered concomitantly with phenothiazines and many other tranquilizers since they potentiate the action of DEMEROL.

All doses of opioids carry an inherent risk of fatal or non-fatal adverse events. This risk is increased with higher doses. 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 AND ADMINISTRATION, Adjustment or Reduction of Dosage).

Solutions of meperidine and barbiturates are chemically incompatible.

Recommended Dose and Dosage Adjustment

Patients Not Taking Opioids at The Time of Initiation of DEMEROL (meperidine hydrochloride) Treatment:

Adults: The usual dosage is 50 to 150 mg orally, every 3 to 4 hours as necessary.

Elderly: Dosage should be reduced.

Children (< 18 years old): Safety and efficacy of DEMEROL in pediatric patients have not been established, and it is not recommended in this patient population.

Patients Currently Receiving Opioids

For patients who are receiving an alternate opioid, the "oral meperidine equivalent" of the analgesic presently being used, should be determined. Having determined the total daily dosage of the present analgesic, Table 1 can be used to calculate the approximate daily oral meperidine dosage that should provide equivalent analgesia. It is usually appropriate to treat a patient with only one opioid at a time. Further dose reductions should be considered due to incomplete cross-tolerance between opioids.

Opioid Rotation: 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 CONVERSION TABLE^a

Opioids	To convert to oral morphine equivalent, multiply by	To convert from oral morphine, multiply by	Daily 90 mg MED^b
Morphine	1	1	90 mg/d
Codeine	0.15	6.67	600 mg/d
Hydromorphone	5	0.2	18 mg/d
Meperidine	0.1	10	900 mg/d
Oxycodone	1.5	0.667	60 mg/d
Tapentadol	0.3-0.4	2.5-3.33	300 mg/d
Tramadol	0.1-0.2	6	***
Methadone	Morphine dose equivalence is not reliably established		

*** The maximum recommended daily dose of tramadol is 300 mg - 400 mg depending on the formulation.

a. Adapted from the 2017 Canadian guideline for opioids for chronic non-cancer pain. McMaster University; 2017

b. MED: Morphine Equivalent Dose

Patients with Hepatic Impairment:

DEMEROL should be given with caution and the initial dose should be reduced in patients with severe impairment of hepatic function.

Patients with Renal Impairment:

DEMEROL should be given with caution and the initial dose should be reduced in patients with severe impairment of renal function.

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** and **ACTION AND CLINICAL PHARMACOLOGY**).

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, gooseflesh, 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.

The 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.

Opioid analgesics may only be partially effective in relieving dysesthetic pain, postherpetic neuralgia, stabbing pains, activity-related pain and some forms of headache. That is not to say that patients with advanced cancer suffering from some of these forms of pain should not be given an adequate trial of opioid analgesics, but it may be necessary to refer such patients at an early time to other forms of pain therapy.

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.

DEMEROL should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended. Unused or expired DEMEROL should be properly disposed of as soon as it is no longer needed to prevent accidental exposure to others, including children or pets. If temporary storage is required before disposal, a sealed child-proof container, such as a biohazard waste container or a lockable medication box could be obtained from a pharmacy.

Missed Dose

If the patient forgets to take one or more doses, they should take their next dose at the next scheduled time and in the normal amount.

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, DEMEROL 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, myosis, hypothermia, skeletal muscle flaccidity, cold and clammy skin and sometimes bradycardia and hypotension.

Treatment: In severe overdosage, particularly by the i.v. route, apnea, circulatory collapse, cardiac arrest and death may occur. 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 HCl 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 HCl should be administered, preferably i.v. 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 (CNS), meperidine resembles but is not identical to morphine.

In its effects on the cardiovascular system, meperidine generally resembles morphine. 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.

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 equianalgesic 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 nonpregnant 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.

Central Nervous System:

Meperidine hydrochloride 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 CO₂ tension and to electrical stimulation.

Meperidine hydrochloride 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 hydrochloride 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 oxycodone overdose.

Gastrointestinal Tract and Other Smooth Muscle:

Meperidine hydrochloride 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.

Cardiovascular System:

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

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

Absorption:

Peak concentrations in the plasma are usually observed in 1 to 2 hours. Analgesic effects are detectable within about 15 minutes following oral administration, reaching a peak within about 2 hours and subsiding gradually over several hours thereafter. In clinical use, the duration of effective analgesia is about 3 to 5 hours.

Oral bioavailability of meperidine is about 40 to 60%.

Distribution:

Approximately 60% is bound to plasma proteins.

Metabolism:

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. 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 to 20 hours) than its parent molecule. Normeperidine has an excitatory effect on the CNS, which is linked to tremors, muscle twitches, and seizures observed in patients with overdosage. In the presence of renal insufficiency, normeperidine elimination is reduced.

Excretion:

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: Individuals under 18 years of age should not take DEMEROL tablets /other formulations.

Geriatrics:

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, Recommended Dose and Dosage Adjustment, Elderly**).

STORAGE AND STABILITY

Store between 15 and 30°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Composition:

Each white tablet with stylized W on one side, scored on the other with D above and 35 below, contains: meperidine HCl 50 mg.

Nonmedicinal ingredients: calcium phosphate (dibasic), calcium sulfate, corn starch, stearic acid and talc. Gluten, lactose-, sucrose- and tartrazine-free.

Packaging:

Bottles of 100

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:

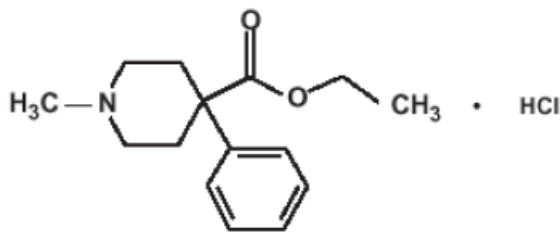
Meperidine hydrochloride

Chemical name:

4-Piperidinecarboxylic acid, 1-methyl-4-phenyl-, ethyl ester, hydrochloride

Molecular formula and molecular mass:

$C_{15}H_{21}NO_2 \cdot HCl$ 283.79

Structural formula:**Physicochemical Properties:**

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

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

® DEMEROL®

(meperidine hydrochloride tablets)

Read this carefully before you start taking DEMEROL and each time you get a refill. 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.**
- **When you take DEMEROL it must be swallowed whole. Do not cut, break, crush, chew, or dissolve the tablet. This can be dangerous and can lead to death or seriously harm you.**
- **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.**
- **You should never give anyone your DEMEROL. They could die from taking it. 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 used to manage 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.

What are the ingredients in DEMEROL?

Medicinal ingredients: meperidine HCl

Non-medicinal ingredients: calcium phosphate (dibasic), calcium sulfate, corn starch, stearic acid and talc. Gluten-, lactose-, sucrose- and tartrazine-free.

DEMEROL comes in the following dosage forms:

Tablets, 50 mg

Do not use DEMEROL if:

- your doctor did not prescribe it for you
- you are allergic to meperidine hydrochloride or any of the other ingredients in DEMEROL (see **What are the 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 tachycardias (a heart rhythm disorder)
- convulsive disorders
- 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
- you are pregnant or planning to become pregnant or you are in labour
- suffer from migraines

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 antidepressants 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)
- skeletal muscle relaxants
- 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
- anti-retroviral drugs (used to treat viral infections e.g. ritonavir, acyclovir)
- anti-epileptic drugs (used to treat epilepsy e.g. phenytoin)
- histamine H₂ receptor antagonist drugs (used in the treatment of heartburn and peptic ulcers e.g. cimetidine)
- drugs such as buprenorphine, nalbuphine, pentazocine may decreased analgesic effect of DEMEROL.
- some heart medication (such as beta blockers)
- drugs used to treat migraines (e.g. triptans)
- St John's Wort

How to take DEMEROL:

Swallow whole. Do not cut, break, crush, chew or dissolve the tablet. This can be dangerous and can lead to death or seriously harm you.

Usual Adult Starting Dose:

Your dose is tailored/personalized just for you. Be sure to follow your doctor's dosing instructions exactly. Do not increase or decrease your dose without consulting your doctor.

Your doctor will prescribe the lowest dose that works to control your pain. 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.

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. Therefore, it is important that you contact your doctor before your current supply runs out.

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

Missed Dose:

If you miss one dose, take it as soon as possible. However, if it is almost time for your next dose, then skip the missed dose. Do not take two doses at once. If you miss several doses in a row, talk to your doctor before restarting your medication.

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			✓

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	
UNKNOWN FREQUENCY Heart: heart attack (in the context of Kounis syndrome), with symptoms such as: tightness, pain, or a squeezing or aching sensation in your chest or arms that may spread to your neck, jaw or back; nausea, heartburn or abdominal pain; shortness of breath; cold sweat; fatigue; sudden dizziness.			✓

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

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. 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 15 and 30°C.**
- **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.**

Disposal:

DEMEROL should never be thrown into household trash, where children and pets may find it. It should be returned to a pharmacy for proper disposal.

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>); the manufacturer's website www.sanofi.ca, or by calling 1-800-265-7927.

This leaflet was prepared by sanofi-aventis Canada Inc.

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