NEW ZEALAND DATA SHEET

WARNINGS

Limitations of use

Because of the risks associated with the use of opioids, pethidine should only be used in patients for whom other treatment options, including non-opioid analgesics, are ineffective, not tolerated or otherwise inadequate to provide appropriate management of pain (see section 4.4).

Hazardous and harmful use

Pethidine poses risks of hazardous and harmful use which can lead to overdose and death. Assess the patient's risk of hazardous and harmful use before prescribing and monitor the patient regularly during treatment (see section 4.4).

Life-threatening respiratory depression

Serious, life-threatening or fatal respiratory depression may occur with the use of pethidine. Be aware of situations which increase the risk of respiratory depression, modify dosing in patients at risk and monitor patients closely, especially on initiation or following a dose increase (see section 4.4).

Concomitant use of benzodiazepines and other central nervous system (CNS) depressants, including alcohol

Concomitant use of opioids with CNS depressants medicines, such as other opioid analgesics, benzodiazepines, gabapentinoids, cannabis, sedatives, hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, centrally-active anti-emetics, general anaesthetics, tranquilisers, or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Limit dosages and durations to the minimum required; and monitor patients for signs and symptoms of respiratory depression and sedation. Caution patients not to drink alcohol while using pethidine (see section 4.4).

1. PRODUCT NAME

DBL™ Pethidine Hydrochloride Injection 50 mg/mL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DBL Pethidine Hydrochloride Injection is available as a 50 mg/1 mL, 75 mg/1.5 mL, and 100 mg/2 mL solution.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Pethidine hydrochloride is a white crystalline powder, very soluble in water and freely soluble in alcohol.

DBL Pethidine Hydrochloride Injection is a sterile, clear solution of pethidine hydrochloride and sodium hydroxide in water for injection. The pH of the injection ranges between 3.5 and 6.0.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DBL Pethidine Hydrochloride Injection is indicated for administration as an anaesthetic adjunct and for obstetric analgesia.

DBL Pethidine Hydrochloride Injection is also indicated for the short-term (24 to 36 hours) management of severe pain for which other treatment options have failed, are contraindicated, not tolerated or are otherwise inappropriate to provide sufficient management of pain. It can be given via the following routes of administration – intramuscular, subcutaneous, slow intravenous bolus injection, intravenous infusion and patient-controlled analgesia (PCA).

4.2 Dose and method of administration

Dose

Adult dosage

1. Analgesia

Dosage should be adjusted according to the severity of pain and the response of the patient and also depends on patient profile e.g., age, weight, sex, previous exposure to narcotics.

25 to 100 mg by intramuscular (preferred) or subcutaneous injection, every 3 to 4 hours.

25 to 50 mg slow intravenous injection, every 3 to 4 hours (see section 4.4).

Usual dose is 200 mg/day by the intravenous route.

Intravenous injection should be made very slowly, preferably using a diluted solution.

For continuous intravenous infusion adequate analgesia should be established prior to commencement of the infusion. A dosage of 0.3 mg/kg/hr is recommended as the initial intravenous infusion rate.

Clinical experience suggests that patients with normal renal function receiving more than 1000 mg/24 hrs pethidine are at particular risk of developing pethidine associated

neurotoxicity (PAN). Patients receiving over 800 mg/24 hrs pethidine should usually be monitored for early signs of norpethidine toxicity (see section 4.4).

Note: *Pethidine associated neurotoxicity is dose related, so pethidine should not be used for periods greater than 24 to 36 hours* (see section 4.4).

2. Obstetric analgesia

50 to 100 mg by intramuscular (preferred) or subcutaneous injection, administered when pain becomes regular. May be repeated 3 to 4 times at one to three-hour intervals if necessary.

Note: *Maximum of 4 doses in 24 hours*

3. Anaesthesia adjunct

As premedication, intramuscular (preferred) or subcutaneous, 50 to 100 mg thirty to ninety minutes prior to anaesthesia.

As an adjunct to anaesthesia, intravenous, by repeated slow injection of fractional doses of a solution diluted to 10 mg per mL. See section 4.4, prior to administering by the intravenous route. Dosage by this route should not exceed 25 to 50 mg.

Note: *Dosage must be titrated to the needs of the patient, depending on the premedication given, the type of anaesthesia, and the nature and duration of the surgical procedure.*

4. Patient-controlled analgesia

Patient-controlled analgesia (PCA) allows patients to assess their own level of pain and consequently titrate the amount of pethidine they require for adequate pain control against sedation and other side effects. Adequate analgesia should be established prior to commencement of PCA.

The dosages and time intervals are pre-set into a microprocessor-controlled infusion pump. When the patient experiences pain, a button is depressed by the patient and a dose of pethidine is administered intravenously. If the patient should depress the button before the pre-set time interval (lockout interval) has elapsed, no extra drug is administered. For adults, demand doses of 5 mg to a maximum of 20 mg pethidine have been given via PCA using a lockout interval of 6 to 20 minutes. Along with the self-administered dose of pethidine, some syringe pumps also deliver a background continuous infusion of pethidine at a basal rate. Some PCA pumps allow a maximum dosage over a defined period to be pre-set in order to avoid patient overdosage.

The demand dosage and lockout interval should be determined according to the patient's analgesic requirements. Patients receiving a background infusion of pethidine should generally receive a smaller demand dose relative to equivalent patients utilising a demand dose only.

Clinical experience suggests that patients with normal renal function receiving more than 1000 mg/24 hrs pethidine are at particular risk of developing pethidine associated neurotoxicity (PAN). Patients receiving over 800 mg/24 hrs pethidine should usually be monitored for early signs of norpethidine toxicity (see section 4.4).

Note: *Pethidine associated neurotoxicity is dose related, so pethidine should not be used for periods greater than 24 to 36 hours, see section 4.4.*

Paediatric dose

1. Children

Analgesia: Intramuscular (preferred) or subcutaneous, 0.5 to 2 mg per kg of body weight, not to exceed 100 mg, every three to four hours as needed.

Pre-operative: Intramuscular (preferred) or subcutaneous, 1 to 2 mg per kg of body weight, not to exceed 100 mg, thirty to ninety minutes prior to anaesthesia.

2. Neonates (see sections 5.1 and 4.6)

Excretion and metabolism of pethidine in the neonate is reduced compared with adults. Safety has not been established in neonates and due to lack of data, no dosage regimen can be recommended.

Geriatric patients

Dose reduction to half normal adult dose is recommended in geriatric patients (over 70 years).

Dose adjustments

Hepatic impairment

Dosage reduction and/or increased dosage intervals are recommended.

Renal impairment

Due to the possibility of accumulation of norpethidine in patients with renal failure, caution should be exercised when pethidine is administered to these patients, especially over prolonged periods of time. Therefore, a decrease in the dose or increase in the dosing interval is recommended (see section 4.4).

Dose conversion

Pethidine, when given intramuscularly in a dose of 75 to 100 mg is equivalent in analgesic effect to the following:

Codeine phosphate	120 mg
Fentanyl citrate	200 micrograms
Morphine	10 mg
Methadone hydrochloride	8 to 10 mg

Method of administration

DBL Pethidine Hydrochloride Injection can be given via the following routes of administration: intramuscular, subcutaneous, slow intravenous bolus injection, intravenous infusion and patient-controlled analgesia (PCA).

An opioid antagonist and facilities for administration of oxygen and control of respiration should be immediately available during and immediately following intravenous administration of pethidine.

Instructions to be given to patient

CNS depression is increased when pethidine is co-administered with CNS depressants, such as other opioid analgesics, benzodiazepines, gabapentinoids, cannabis, sedatives, hypnotics, tricyclic antidepressants, antipsychotics (e.g., butyrophenones, phenothiazines), antihistamines, centrally-active anti-emetics, general anaesthetics, tranquilisers, other CNS depressants, and alcohol.

Driving and operating dangerous machinery should not be contemplated until the day following the last dose of pethidine.

4.3 Contraindications

Hypersensitivity to pethidine.

Severe respiratory disease, acute respiratory disease, respiratory depression, or where respiratory reserve is depleted (acute bronchial asthma, chronic airway disease, severe emphysema, severe chronic bronchitis, kyphoscoliosis).

Head injury, raised intracranial pressure (apart from introducing monitoring and diagnostic problems, hypercapnia associated with respiratory depression can itself result in elevated intracranial pressure), brain tumour.

Cardiac arrhythmias, especially supraventricular tachycardias, cor pulmonale. Pethidine has a vagolytic action and may produce a significant increase in the ventricular response rate.

Concurrent use of monoamine oxidase inhibitors (MAOIs), including selegiline, or use of MAOIs within two weeks prior. The combination of MAOIs and pethidine has caused hypotension, hypertension, excitation, rigidity, hyperpyrexia and/or convulsions and in some cases, fatalities have been reported. This combination should be avoided.

Pre-eclampsia, eclampsia.

Convulsive states such as status epilepticus, tetanus and strychnine poisoning, due to the stimulatory effects of pethidine on the spinal cord.

Diabetic acidosis where there is a danger of coma.

Acute alcoholism or delirium tremens.

Severe liver disease, incipient hepatic encephalopathy.

Patients with a low platelet count, coagulation disorders or receiving anticoagulant treatment.

Known or suspected gastrointestinal obstruction, including paralytic ileus (see section 4.4).

Continuous intravenous infusion: The administration of pethidine via continuous intravenous infusion in patients with renal impairment is contraindicated.

Patient-controlled analgesia: The administration of pethidine via patient-controlled analgesia (PCA) in young children and adults with poor cognitive function is contraindicated. The administration of pethidine via PCA in patients with renal impairment is contraindicated.

4.4 Special warnings and precautions for use

Therapy should only be initiated by a specialist with experience in chronic pain management and in accordance with guidelines approved by the New Zealand Medical Council.

Hazardous and harmful use

DBL Pethidine Hydrochloride Injection contains the opioid pethidine hydrochloride and is a potential drug of abuse, misuse and addiction. Addiction can occur in patients appropriately prescribed pethidine at recommended doses.

The risk of addiction is increased in patients with a personal or family history of substance abuse (including alcohol and prescription and illicit drugs) or mental illness. The risk also increases the longer the drug is used and with higher doses. Patients should be assessed for their risks for opioid abuse or addiction prior to being prescribed pethidine.

All patients receiving opioids should be routinely monitored for signs of misuse and abuse. Opioids are sought by people with addiction and may be subject to diversion. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the safe storage and proper disposal of any unused drug (see section 6.6). Caution patients that abuse of oral or transdermal forms of opioids by parenteral administration can result in serious adverse events, which may be fatal.

Patients should be advised not to share pethidine with anyone else.

Accidental ingestion/exposure

Accidental ingestion or exposure of pethidine, especially by children, can result in a fatal overdose of pethidine. Patients and their caregivers should be given information on safe storage and disposal of unused pethidine (see section 6.6).

Life-threatening reactions

Serious or life-threatening reactions such as respiratory depression, coma, convulsions, possibly due to elevated levels of norpethidine and hypotension have been associated with the use of pethidine. Therefore, the recommendations in this section should be carefully observed.

Respiratory depression

Serious, life-threatening or fatal respiratory depression can occur with the use of opioids even when used as recommended. It can occur at any time during the use of pethidine, but the risk is greatest during initiation of therapy or following an increase in dose. Patients should be monitored closely for respiratory depression at these times.

The risk of life-threatening respiratory depression is also higher in elderly, frail, or debilitated patients and in patients with existing impairment of respiratory function (e.g., chronic obstructive pulmonary disease; asthma) and hepatic and renal impairment. Opioids should be

used with caution and with close monitoring in these patients (see section 4.2). The use of opioids is contraindicated in patients with severe respiratory disease, acute respiratory disease and respiratory depression (see section 4.3).

The risk of respiratory depression is greater with the use of high doses of opioids, especially high potency and modified release formulations, and in opioid naïve patients. Initiation of opioid treatment should be at the lower end of the dosage recommendations with careful titration of doses to achieve effective pain relief. Careful calculation of equianalgesic doses is required when changing opioids or switching from immediate release to modified release formulations together with consideration of pharmacological differences between opioids. Consider starting the new opioid at a reduced dose to account for individual variation in response (see section 4.2).

In addition, large doses and/or rapid intravenous administration of pethidine may produce rapid onset respiratory depression including central sleep apnoea (CSA) and sleep-related hypoxaemia, apnoea, hypotension, peripheral circulatory collapse, bradycardia (as a result of stimulation of medullary vagal nuclei) or even cardiac arrest. Pethidine should not be administered by intravenous injection unless an opioid antagonist and facilities for controlled or assisted respiration are available. Consider decreasing the opioid dosage using best practices for opioid taper.

Patients with severe pain may tolerate very high doses of pethidine but may exhibit respiratory depression should their pain suddenly subside.

Seizures

Seizures may result from prolonged exposure or high doses of pethidine due to pethidine associated neurotoxicity (PAN). PAN is a recognised clinical entity which is mainly due to the metabolite norpethidine (see section 4.8). Norpethidine concentrations are enhanced by reduction in renal excretion as in the elderly and the very young and by increased conversion of pethidine to norpethidine due to the effects of drugs such as phenobarbitone and phenytoin. Furthermore, pethidine associated neurotoxicity is dose related, so pethidine should not be used for periods greater than 24 to 36 hours. Refer to Pethidine associated neurotoxicity (PAN) below.

Pethidine may aggravate pre-existing convulsions in patients with convulsive disorders. If dosage is escalated substantially above recommended levels because of tolerance development, convulsions may occur in individuals without a history of convulsive disorders.

Pethidine associated neurotoxicity (PAN)

The risk of pethidine associated neurotoxicity (PAN) is increased in a situation in which the patient may receive large doses of pethidine, as with patient-controlled analgesia (PCA). Caution should therefore be taken in patients receiving pethidine by PCA. Frequent clinical assessment and recording of the amount of drug used is required to minimise such risks. Clinical experience suggests that patients with normal renal function receiving more than 1000 mg/24 hrs pethidine are at particular risk of developing PAN. Patients receiving over 800 mg/24 hrs pethidine should be usually monitored for early signs of norpethidine toxicity (e.g., twitching, anxiety).

Serotonin syndrome

The development of serotonin syndrome (SS), which is potentially life-threatening, has been reported with opioid use, including with pethidine. Serotonin syndrome generally occurred when pethidine was used concomitantly with serotonergic drugs (see section 4.5).

Serotonin syndrome may include mental status changes (e.g., agitation, hallucinations, coma, confusion), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia, diaphoresis), neuromuscular abnormalities (e.g., hyperreflexia, incoordination, rigidity, tremor, myoclonus), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea).

If serotonin syndrome is suspected, a dose reduction or discontinuation of at least one of the serotonergic medicines being taken should be considered depending on the severity of symptoms.

Patients with head injuries or acute abdominal conditions

Opioids may obscure the diagnosis and/or mask the clinical course of patients with head injuries or acute abdominal conditions and should not be used unless absolutely necessary in these conditions. The respiratory depressant effects of pethidine may be markedly exaggerated in the presence of head injury.

Inadvertent intra-arterial administration

Inadvertent intra-arterial administration can produce severe necrosis and gangrene.

Reduced cardiac output

Reduced cardiac output may lead to reduced hepatic perfusion and diminished metabolism of pethidine leading to accumulation of pethidine with possible toxic results.

Orthostatic hypotension

Orthostatic hypotension has been reported in ambulatory patients administered pethidine.

Pain relief in cardiac infarction

Pethidine may cause a transient rise in blood pressure and systemic vascular resistance and increased heart rate. Therefore, it is not recommended for pain relief in cardiac infarction.

Patients with pheochromocytoma

Pethidine in patients with pheochromocytoma may result in a hypertensive crisis.

Patients with eclampsia

In eclampsia, the combination of pethidine with phenothiazines has been reported to induce recurrence of seizures rather than stopping them. Therefore, the use of pethidine in eclampsia and pre-eclampsia is contraindicated (see sections 4.3, 4.5 and 4.6).

Pain relief in obstetrics

Pethidine, while commonly used for pain relief in obstetrics, is known to pass the placenta and may cause neonatal depression, including respiratory depression. An opioid antagonist such as naloxone may be required to reverse such depression. In the neonate, pethidine is excreted and metabolised at a significantly reduced rate compared to adults.

Prostatic hypertrophy or urethral stricture

Pethidine should be used with caution in patients with prostatic hypertrophy or urethral stricture.

Hypoglycaemia/hyperglycaemia

Hypoglycaemia and hyperglycaemia have been reported during opioid use. This effect should be considered when diabetics require pethidine.

Ophthalmic effects

There are conflicting reports about the effect of pethidine on the eye. Some reports state that pethidine and its congeners produce miosis, whereas others indicate that these drugs tend to produce mydriasis or no pupillary change. Until the effects are better defined intraocular tension should be monitored in patients with glaucoma who received pethidine.

Tolerance, dependence and withdrawal

Neuroadaptation of the opioid receptors to repeated administration of opioids can produce tolerance and physical dependence. Tolerance is the need for increasing doses to maintain analgesia. Tolerance may occur to both the desired and undesired effects of the opioid.

Physical dependence, which can occur after several days to weeks of continued opioid usage, results in withdrawal symptoms if the opioid is ceased abruptly or the dose is significantly reduced. Withdrawal symptoms can also occur following the administration of an opioid antagonist (e.g., naloxone) or partial agonist (e.g., buprenorphine). Withdrawal can result in some or all of the following symptoms: dysphoria, restlessness/agitation, lacrimation, rhinorrhoea, yawning, sweating, chills, myalgia, mydriasis, irritability, anxiety, increasing pain, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhoea, increased blood pressure, increased respiratory rate and increased heart rate.

When discontinuing pethidine in a person who may be physically dependent, the drug should not be ceased abruptly but withdrawn by tapering the dose gradually (see Ceasing opioids and section 4.2).

In an individual physically dependent on opioids, the administration of the usual dose of an opioid antagonist will precipitate an acute withdrawal syndrome. The severity of this syndrome will depend on the degree of physical dependence and the dose of antagonist administered. The use of opioid antagonists in such individuals should be avoided if possible. If an opioid antagonist must be used to treat serious respiratory depression in the physically dependent patient, the antagonist should be administered with extreme care and only 10 to 20% of the usual initial dose administered.

Ceasing opioids

Abrupt discontinuation or rapid decreasing of the dose in a person physically dependent on an opioid may result in serious withdrawal symptoms and uncontrolled pain (see Tolerance, dependence and withdrawal). Such symptoms may lead the patient to seek other sources of licit or illicit opioids. Opioids should not be ceased abruptly in a patient who is physically dependent but withdrawn by tapering the dose slowly. Factors to take into account when deciding how to discontinue or decrease therapy include the dose and duration of the opioid the patient has been using, the type of pain being treated and the physical and psychological attributes of the patient. A multimodal approach to pain management should be in place before initiating an opioid analgesic taper. During tapering, patients require regular review and support to manage any increase in pain, psychological distress and withdrawal symptoms.

There are no standard tapering schedules suitable for all patients and an individualised plan is necessary. In general, tapering should involve a dose reduction of no more than 10 percent to 25 percent every 2 to 4 weeks (see section 4.2). If the patient is experiencing increased pain or serious withdrawal symptoms, it may be necessary to go back to the previous dose until stable before proceeding with a more gradual taper.

When ceasing opioids in a patient who has a suspected opioid use disorder, the need for medication assisted treatment and/or referral to a specialist should be considered.

Neonatal opioid withdrawal syndrome

Refer to section 4.6.

Use of opioids in chronic (long-term) non-cancer pain (CNCP)

Opioid analgesics have an established role in the treatment of acute pain, cancer pain and palliative and end-of-life care. Current evidence does not generally support opioid analgesics in improving pain and function for most patients with chronic non-cancer pain. The development of tolerance and physical dependence and risks of adverse effects, including hazardous and harmful use, increase with the length of time a patient takes an opioid. The use of opioids for long-term treatment of CNCP is not recommended.

The use of an opioid to treat CNCP should only be considered after maximised non-pharmacological and non-opioid treatments have been tried and found ineffective, not tolerated or otherwise inadequate to provide sufficient management of pain. Opioids should only be prescribed as a component of comprehensive multidisciplinary and multimodal pain management.

Opioid therapy for CNCP should be initiated as a trial in accordance with clinical guidelines and after a comprehensive biopsychosocial assessment has established a cause for the pain and the appropriateness of opioid therapy for the patient (see Hazardous and harmful use). The expected outcome of therapy (pain reduction rather than complete abolition of pain, improved function and quality of life) should be discussed with the patient before commencing opioid treatment, with agreement to discontinue treatment if these objectives are not met.

Owing to the varied response to opioids between individuals, it is recommended that all patients be started at the lowest appropriate dose and titrated to achieve an adequate level of analgesia and functional improvement with minimum adverse reactions. Immediate-release products

should not be used to treat chronic pain but may be used for a short period in opioid naïve patients to develop a level of tolerance before switching to a modified-release formulation. Careful and regular assessment and monitoring is required to establish the clinical need for ongoing treatment. Discontinue opioid therapy if there is no improvement of pain and/or function during the trial period or if there is any evidence of misuse or abuse. Treatment should only continue if the trial has demonstrated that the pain is opioid responsive and there has been functional improvement. The patient's condition should be reviewed regularly, and the dose tapered off slowly if opioid treatment is no longer appropriate (see Ceasing opioids).

Hyperalgesia

Hyperalgesia may occur with the use of opioids, particularly at high doses. Hyperalgesia may manifest as an unexplained increase in pain, increased levels of pain with increasing opioid dosages or diffuse sensitivity not associated with the original pain. Hyperalgesia should not be confused with tolerance (see Tolerance, dependence and withdrawal). If opioid induced hyperalgesia is suspected, the dose should be reduced and tapered off if possible. A change to a different opioid may be required.

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.

Patients with hypothyroidism or Addison's disease

Pethidine should be given with caution and the initial dose should be reduced in patients with hypothyroidism or Addison's disease.

Risks of use in patients with gastrointestinal conditions

Pethidine is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.

Because of the spasmogenic properties of pethidine on the biliary tract and sphincter of Oddi, it should be used only when necessary and then with caution in biliary colic, operations on the biliary tract and acute pancreatitis. Pethidine may render surgical exploration of the common bile duct difficult.

Decreased gastric emptying associated with pethidine may be expected to increase the risks of aspiration either associated with pethidine induced CNS depression/coma or during or after general anaesthesia, e.g., a labouring patient who proceeds to caesarean section.

Patients with severe inflammatory bowel disease

The risk of toxic megacolon may be increased in patients with severe inflammatory bowel disease.

Use in patient-controlled analgesia (PCA)

The use of pethidine in patient-controlled analgesia (PCA) should be reserved for short-term (24 to 36 hours) use in patients with normal renal function who have adverse reactions to morphine. Morphine is the opioid of choice for PCA.

Risks of concomitant use or discontinuation of cytochrome P450 3A4 inhibitors and inducers

Concomitant use of pethidine with a CYP3A4 inhibitor, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may increase plasma concentrations of pethidine and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression (see Respiratory depression) particularly when an inhibitor is added after a stable dose of pethidine is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampicin, carbamazepine, and phenytoin, in pethidine treated patients may increase pethidine plasma concentrations and prolong opioid adverse reactions. When using pethidine with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in pethidine treated patients, monitor patients closely at frequent intervals and consider dosage reduction of pethidine until stable drug effects are achieved (see section 4.5).

Concomitant use of pethidine with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease pethidine plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to pethidine. When using pethidine with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider adjusting the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur (see section 4.5).

Risks from concomitant use of benzodiazepines or other CNS depressants, including alcohol

Concomitant use of opioids and benzodiazepines or other CNS depressants, including alcohol, may result in sedation, respiratory depression including CSA and sleep related hypoxaemia, coma and death. Because of these risks, concomitant prescribing of pethidine with CNS depressant medicines, such as other opioid analgesics, benzodiazepines, gabapentinoids, cannabis, sedatives, hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, centrally-active anti-emetics, general anaesthetics, tranquilisers, or other CNS depressants, should be reserved for patients for whom other treatment options are not possible.

If a decision is made to prescribe pethidine concomitantly with any of the medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible. 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. Patients should be followed closely for signs and

symptoms of respiratory depression and sedation. Patients and their caregivers should be made aware of these symptoms. Patients and their caregivers should also be informed of the potential harms of consuming alcohol while using pethidine.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of medicine-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 section 4.5).

Advise both patients and caregivers about the risks of respiratory depression including CSA and sleep-related hypoxaemia, and sedation when pethidine is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery during concomitant use of the benzodiazepine or other CNS depressant. These activities should not be contemplated until the day following the last dose of pethidine (see section 4.7). 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 section 4.5).

Fatal interaction with monoamine oxidase inhibitors

Pethidine is contraindicated in patients who are receiving monoamine oxidase (MAO) inhibitors or those who have recently received such agents. Therapeutic doses of pethidine 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 pre-existing hyperphenylalaninemia. Some have been characterised by coma, severe respiratory depression, cyanosis, and hypotension, and have resembled the syndrome of acute narcotic overdose. Serotonin syndrome with agitation, hyperthermia, diarrhoea, tachycardia, sweating, tremors and impaired consciousness may also occur. In other reactions the predominant manifestations have been hyperexcitability, convulsions, tachycardia, hyperpyrexia, and hypertension.

Do not use pethidine in patients taking MAOIs or within 14 days of stopping such treatment.

Use in hepatic/renal impairment

Since pethidine is metabolised in the liver and excreted via the kidneys, the possibility of accumulation of the toxic metabolite norpethidine should be considered in patients with hepatic and/or renal impairment (see section 4.2).

Use in the elderly

The elderly demonstrate an increased sensitivity to opioids relative to younger patients. Reduced liver function, renal function and plasma protein binding may contribute to the elevated plasma levels found in elderly subjects.

Paediatric use

Norpethidine concentrations are enhanced by reduction in renal excretion as in the very young and in the elderly (see Seizures, Pethidine associated neurotoxicity (PAN) and section 4.2).

4.5 Interaction with other medicines and other forms of interaction

Pethidine has been found to interact with the following drugs:

Barbiturates, chloral hydrate, benzodiazepines: Pethidine enhances the CNS depressant effects of these drugs. In addition, the combination of pethidine and phenobarbitone may reduce the analgesic effect of pethidine in part due to the increased conversion of pethidine to the toxic metabolite, norpethidine.

Benzodiazepines and other central nervous system (CNS) depressants	
Clinical impact	Due to the additive pharmacologic effect, the concomitant use of pethidine with CNS depressant medicines, such as other opioid analgesics, benzodiazepines, gabapentinoids, cannabis, sedatives, hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, centrally-active anti-emetics, general anaesthetics, tranquilisers, or other CNS depressants including alcohol, increases the risk of respiratory depression, profound sedation, coma, and death.
Intervention	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation (see section 4.4).
Examples	CNS depressant medicines, such as other opioid analgesics, benzodiazepines, gabapentinoids, cannabis, sedatives, hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, centrally-active anti-emetics, general anaesthetics, tranquilisers, other CNS depressants including alcohol.

Phenothiazines: CNS toxicity and hypotension including respiratory depression may occur when given together. In eclampsia the combination has been reported to induce recurrence of seizures (see sections 4.3, 4.4 and 4.6).

Butyrophenones: The CNS depressant effect of tranquillisers may be increased by pethidine.

Paracetamol: Absorption may be reduced due to delayed gastric emptying caused by pethidine.

CNS depressants (including alcohol): Depressant effects may be enhanced by pethidine.

Phenytoin: Increased metabolism of pethidine and generation of norpethidine resulting in the possibility of increased CNS effects of norpethidine and reduced analgesia.

The effects of **coumarin or indandione** – derivative anticoagulants may be increased.

Concurrent use with **amphetamines**, which have some MAO inhibiting activity is not recommended because of the risk of serious reactions similar to those reported with other MAO inhibitors.

Serotonergic drugs: The concomitant use of opioids including pethidine, with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome (see section 4.4). Drugs that affect the serotonergic neurotransmitter system include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT_3 receptor antagonists, and MAOIs.

Monoamine oxidase inhibitors (MAOIs)	
Clinical impact	Pethidine is contraindicated in patients who are receiving monoamine oxidase (MAO) inhibitors or those who have recently received such agents. Therapeutic doses of pethidine 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 pre-existing hyperphenylalaninemia. Some have been characterised by coma, severe respiratory depression, cyanosis, and hypotension, and have resembled the syndrome of acute narcotic overdose. Serotonin syndrome with agitation, hyperthermia, diarrhoea, tachycardia, sweating, tremors and impaired consciousness may also occur. In other reactions the predominant manifestations have been hyperexcitability, convulsions, tachycardia, hyperpyrexia, and hypertension.
Intervention	Do not use pethidine in patients taking MAOIs or within 14 days of stopping such treatment.
Examples	Phenelzine, tranylcypromine, linezolid.
Inhibitors of CYP3A4 and CYP2B6	
Clinical impact	The concomitant use of pethidine and CYP3A4 or CYP2B6 inhibitors can increase the plasma concentration of pethidine, resulting in increased or prolonged opioid effects. These effects could be more pronounced with concomitant use of pethidine and CYP2B6 and CYP3A4 inhibitors, particularly when an inhibitor is added after a stable dose of pethidine is achieved (see section 4.4). After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the pethidine plasma concentration will decrease (see section 5.2), resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to pethidine.
Intervention	If concomitant use is necessary, consider dosage reduction of pethidine until stable drug effects are achieved. Monitor patients for respiratory depression and sedation at frequent intervals. If a CYP3A4 or CYP2B6 inhibitor is discontinued, consider adjusting the pethidine dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal.

Examples	Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), protease inhibitors (e.g., ritonavir).
CYP3A4 and CYP2B6 inducers	
Clinical impact	The concomitant use of pethidine and CYP3A4 inducers, or CYP2B6 inducers can decrease the plasma concentration of pethidine (see section 5.2), resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to pethidine (see section 4.4). After stopping a CYP3A4 or CYP2B6 inducer, as the effects of the inducer decline, the pethidine plasma concentration will increase (see section 5.2), which could increase or prolong both the therapeutic effects and adverse reactions and may cause serious respiratory depression.
Intervention	If concomitant use is necessary, consider adjusting the pethidine dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal. If a CYP3A4 or CYP2B6 inducer is discontinued, consider pethidine dosage reduction and monitor for signs of respiratory depression.
Examples	Rifampicin, carbamazepine, phenytoin.

4.6 Fertility, pregnancy and lactation

Effects on fertility

No data available.

Use in pregnancy – Category C*

Opioid analgesics may cause respiratory depression in the newborn infant. These products should therefore only be used after weighing the needs of the mother during labour against the risk to the fetus (see also section 5.2 Pharmacokinetic properties - Excretion).

Prolonged use of opioid analgesics during pregnancy can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognised and treated, and requires management according to protocols developed by neonatology experts.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhoea, and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn. Observe newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

In eclampsia the combination of pethidine with phenothiazines has been reported to induce recurrence of seizures rather than stopping them. Therefore, the use of pethidine in eclampsia and pre-eclampsia is contraindicated (see sections 4.3, 4.4 and 4.5).

Animal reproduction studies have not been conducted with pethidine and safe use in pregnancy prior to labour has not been established with regard to possible adverse effects on fetal development.

*Category C = Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible.

Lactation

Pethidine is excreted in breast milk; however, clinical data on the rate of excretion or concentration of pethidine in breast milk is not available. The clinical significance of these findings is yet to be determined. It is not recommended that pethidine be administered to nursing mothers.

4.7 Effects on ability to drive and use machines

Since pethidine may cause drowsiness and general impairment of co-ordination, ambulatory patients should be cautioned against driving or operating machinery. Driving and operating dangerous machinery should not be contemplated until the day following the last dose of pethidine.

4.8 Undesirable effects

As with other opioid analgesics, respiratory depression is the major hazard associated with parenteral pethidine therapy. Other adverse reactions include:

More common reactions

Central nervous system – Light-headedness, dizziness, sedation, sweating, bizarre feelings, disorientation, hallucinations, psychosis. Some of these effects seem to be more prominent in ambulatory patients and those not experiencing severe pain, and may be relieved by reducing the dose slightly and lying down.

Gastrointestinal – Nausea and vomiting, constipation.

Less common reactions

Cardiovascular – Hypotension, vasodilation, hypertension, tachycardia, bradycardia, gangrene, following inadvertent intra-arterial administration.

Dermatological – Rash, pruritus, urticaria, erythema, injection site complications e.g., local irritation and induration, fibrosis of muscle tissue with frequent repetition of intramuscular injection.

Gastrointestinal – Decreased gastric emptying. Cases of oesophageal disorder (e.g., oesophageal motility disorder, lower oesophageal sphincter relaxation impaired, oesophageal peristalsis decreased) have been reported with opioid therapy.

Genito-urinary – Urinary retention and anuria.

Hepatic – Increased biliary tract pressure, choledochoduodenal sphincter spasm.

Nervous system – Pethidine associated neurotoxicity (see section 4.4), or neuropsychiatric toxicity i.e., auditory and visual hallucinations, irritability, agitation, hypomania, paranoia, delirium and complex partial seizures, vertigo, dizziness, coma, headache, convulsions or tremor, respiratory depression, cold clammy skin, sweating and pallor. Inadvertent injection around a nerve trunk may cause sensory-neural effects, which is usually, but not always transitory.

Psychiatric – Neuropsychiatric toxicity, hyperactivity or agitation, depression, mental clouding, dysphoria.

General – Dry mouth, weakness, hypersensitivity.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/.

4.9 Overdose

Signs and symptoms

Opioid analgesic overdosage usually produces central nervous system depression ranging from stupor to a profound coma, respiratory depression which may progress to Cheyne-Stokes respiration and/or cyanosis, cold clammy skin and/or hypothermia, flaccid skeletal muscles, bradycardia and hypotension. In patients with severe overdosage, particularly following rapid intravenous administration of an opioid, apnoea, circulatory collapse, cardiac arrest, respiratory arrest and death may occur.

Complications such as pneumonia, shock and/or pulmonary oedema may also prove fatal. Although miosis (pupillary constriction) is characteristic of overdosage with morphine derivatives and methadone, mydriasis may occur in terminal narcosis or severe hypoxia. Overdosage of pethidine may produce mydriasis rather than miosis.

Toxic effects of pethidine may be excitatory, especially in patients who have developed tolerance to the depressant effects of the drug. These patients may exhibit dry mouth, increased muscular activity, muscle tremors and twitches, tachycardia, delirium with disorientation, hallucinations and, occasionally, grand mal seizures.

Treatment

In overdosage, if necessary, establish an airway and institute assisted or controlled ventilation.

Circulation should be maintained with infusions of plasma or suitable electrolyte solution. If consciousness is impaired and respiration depressed, an opioid antagonist should be administered. Naloxone, a pure antagonist, is now the treatment of choice. Consult naloxone

(or nalorphine) product information. Administer naloxone (e.g., 0.4 mg) intravenously which may be repeated at 2 to 3-minute intervals. For children, the initial dose recommended is 0.01 mg/kg naloxone. In neonates, a more rapid and improved antagonism was noted after 0.02 mg/kg was administered. A response should be seen after 2 or 3 doses. Note the duration of action of naloxone is usually shorter than that of pethidine and thus the patient should be carefully observed for signs of CNS depression returning. An opioid antagonist should not be administered in the absence of clinical signs of respiratory or cardiovascular depression.

Note: In an individual physically dependent on opioids, the administration of the usual dose of an opioid antagonist will precipitate an acute withdrawal syndrome. The severity of this syndrome will depend on the degree of physical dependence and the dose of antagonist administered. The use of opioid antagonists in such individuals should be avoided if possible. If an opioid antagonist must be used to treat serious respiratory depression in the physically dependent patient, the antagonist should be administered with extreme care and only 10 to 20% of the usual initial dose administered.

For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Pethidine is a synthetic opioid analgesic which produces a pattern of effects similar to morphine the standard against which opioid analgesics are compared. In addition to analgesia, the effect of pethidine on the central nervous system causes respiratory depression, drowsiness, sedation, change in mood, euphoria, dysphoria, mental clouding, nausea, vomiting, and electroencephalographic changes. Large doses of pethidine may induce excitation or convulsions. Pethidine is not effective in the management of cough or diarrhoea.

As a general rule, 75 to 100 mg pethidine (parenterally) is equivalent to 10 mg morphine with respect to analgesic effect, euphoria and respiratory depression.

Pethidine has local anaesthetic activity but may be irritant when applied locally.

Opioids exert their pharmacological actions by interaction with stereo-specific opiate receptors located in the central and peripheral nervous systems.

5.2 Pharmacokinetic properties

Absorption: Pethidine may be administered as an intramuscular, intravenous or subcutaneous injection. Variable absorption has been observed in some cases following intramuscular administration. It has been found that 80% or more of a 100 mg dose of pethidine administered intramuscularly is absorbed over six hours with a mean time of maximum plasma concentration at approximately 24 minutes.

Analgesia may persist for two to four hours following intramuscular, intravenous and subcutaneous administration.

Distribution: There is no specific information on the distribution of pethidine, but data indicate that pethidine is extensively distributed extravascularly, primarily into rapidly perfused tissues.

The apparent volume of distribution is estimated as 4.17 L/kg. Plasma protein binding has been estimated to be 64.3%. Because of the large volume of distribution of pethidine, displacement of pethidine from plasma proteins is not likely to cause a significant increase in free pethidine concentration.

Metabolism: Pethidine is extensively metabolised in the liver. It undergoes transformation primarily by hydrolysis to pethidinic acid, followed by partial conjugation with glucuronic acid. Pethidine also undergoes N-demethylation to norpethidine, followed by hydrolysis and partial conjugation. *In vitro* data show pethidine is metabolised to norpethidine in liver mainly by CYP3A4 and CYP2B6.

Norpethidine, a major metabolite, is estimated to be half as active as pethidine as an analgesic but twice as potent as a convulsive agent as pethidine.

Accumulation of pethidine can occur in patients with hepatic dysfunction. Adjustment in dose, frequency and/or duration of pethidine therapy is recommended.

Excretion: The mean plasma clearance of pethidine following intravenous injection is 1.06 L/min (range 0.71 to 1.32) but only 3.8% of the dose is excreted unchanged (range 2.2 to 6.9%). Plasma clearance is significantly reduced with hepatic dysfunction.

Elimination half-life of pethidine has been estimated to be approximately 3.5 hours. This can be prolonged to 7-11 hours in cirrhotic patients and patients with acute viral hepatitis, see Metabolism for advice on dosage adjustment.

In patients with impaired renal function, persons over 60 years and the neonate, the elimination half-life of norpethidine is prolonged from the normal range of 8-21 hours to longer than 30 hours which may lead to accumulation and toxic side effects such as seizures, agitation, irritability, tremors, twitches and myoclonus. The half-life of norpethidine in pregnant women averages 20.6 hours.

Pethidine and norpethidine accumulate in maternal plasma following multiple doses of pethidine during labour and maximum exposure of the fetus will result because of a continued diffusion gradient from mother to fetus. Elimination of both pethidine and norpethidine is prolonged and with long drug-to-delivery intervals and/or multiple doses, the levels of norpethidine in the newborn may become clinically significant.

The urinary excretion of pethidine and norpethidine may be enhanced with acidification of the urine.

5.3 Preclinical safety data

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injection
Sodium hydroxide

6.2 Incompatibilities

The mixing of thiopentone solutions with DBL Pethidine Hydrochloride Injection results in the formation of a pharmacologically inactive complex. A loss of clarity of solution was noted when solutions of DBL Pethidine Hydrochloride Injection were mixed with the following: aminophylline, heparin, amobarbital sodium, methicillin sodium, morphine sulfate, phenobarbital sodium, phenytoin sodium, sodium bicarbonate or sodium iodide.

DBL Pethidine Hydrochloride Injection is also incompatible with alkalis, iodine and iodides.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25°C. Protect from light.

6.5 Nature and contents of container

DBL Pethidine Hydrochloride Injection is available in the following presentations and pack sizes:

Presentations	**Pack sizes**
50 mg in 1 mL	5 Ampoules
75 mg in 1.5 mL	5 and 50 Ampoules
100 mg in 2 mL	5 Ampoules

Not all presentations or pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Controlled Drug (B3)

8. SPONSOR

Pfizer New Zealand Limited
PO Box 3998
Auckland, New Zealand
Toll Free Number: 0800 736 363
www.pfizermedicalinformation.co.nz

9. DATE OF FIRST APPROVAL

08 August 1985

10. DATE OF REVISION OF THE TEXT

19 June 2025

Summary table of changes

Section changed	Summary of new information
4.8	Addition of ADR 'oesophageal disorder'.
Throughout	Minor corrections throughout