NEW ZEALAND DATA SHEET

1. PRODUCT NAME (strength pharmaceutical form)

Pethidine, Tablet, 50 mg (NOUMED) Pethidine, Tablet, 100 mg (NOUMED)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Name and strength of the active substance
Pethidine Hydrochloride 50 mg
Pethidine Hydrochloride 100 mg

Excipient(s) with known effect
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral – tablet

Presentation
Pethidine Hydrochloride 50 mg tablets are: round, white, normal biconvex tablets, 8.0 mm diameter.

Pethidine Hydrochloride 100 mg Tablets are: round, white, normal biconvex tablets, 9.5 mm diameter.

Note: Not all product strengths may be marketed.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Pethidine Tablets given orally are indicated for the relief of most types of moderate to severe pain. As it has some antispasmodic activity, it may be the analgesic of choice in renal colic, biliary colic and acute pancreatitis.

4.2 Dose and method of administration

Adults:
For the relief of pain, Pethidine Tablets given in oral doses of 50 to 150 mg by mouth every 4 hours if necessary.

Children:
For the relief of pain, 1.1 to 1.76 mg per kg of body weight, not to exceed 100 mg every 3 to 4 hours as needed. (See Section 4.4 Special Warnings and Precautions for use).
Opioid agonist analgesics may suppress respiration, especially in the very young,

elderly, very ill or debilitated patients and those with respiratory problems. Lower doses may be required for these patients.

Neonates (see also Pharmacology section 5 and Use in Pregnancy section 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).

Liver 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 also Precautions section 4.4).

Tolerance to many of the effects of opioid analgesics may develop with repeated administration. The first sign of tolerance is a decrease in the duration of adequate analgesia. Careful dosage adjustment is required to maintain analgesic effect.

Psychological and physical dependence may occur with chronic administration of opioid analgesics; and abstinence syndrome may occur when these drugs are discontinued. Physical dependence in patients receiving prolonged therapy for severe chronic pain rarely leads to true addiction. Gradual withdrawal may minimize the development of withdrawal symptoms following prolonged use.

4.3 Contraindications

Pethidine Hydrochloride is contraindicated in the following:

- Hypersensitivity to Pethidine.
- 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 arrythmias, 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 (MAOI's), including selegiline, or use of MAOI's within two weeks prior. The combination of monoamine oxidase inhibitors 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 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.

- Supraventricular tachycardias.

4.4 Special warnings and precautions for use

Warnings

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.

Large doses and/or rapid intravenous administration of Pethidine may produce rapid onset respiratory depression, 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.

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 Undesirable effects). 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.

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 going on the caesarean section.

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 can produce severe necrosis and gangrene.

Opioid analgesics have abuse potential. Psychological and physical dependence may occur with repeated dosing. Pethidine should be restricted to short-term administration for the relief of severe pain not responding to non-opioid analgesics. Abrupt withdrawal of Pethidine in those physically dependent may precipitate withdrawal syndrome, including convulsions.

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

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.

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/24hrs Pethidine are at particular risk of developing PAN. Patients receiving over 800 mg/24hrs Pethidine should be usually monitored for early signs of norpethidine toxicity (e.g., twitching, anxiety).

Serotonin syndrome
The development of serotonin syndrome, 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 Interactions with other medicines and other forms of interactions).

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 the symptoms.

Precautions
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 Sections 4.4 Special Warnings and Precautions for use should be carefully observed. Since Pethidine may cause drowsiness and general impairment of coordination, ambulatory patients should be cautioned against driving or operating machinery.

Pethidine should be used with caution in patients taking other CNS depressant drugs such as hypnotics and sedatives including barbiturates and benzodiazepines, phenothiazines, and other tranquillisers, anaesthetics, alcohol and antidepressants.

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

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.

Since Pethidine is metabolised in the liver and excreted via the kidneys, the possibility of accumulation of the toxic metabolic norpethidine should be considered in patients with hepatic and/or renal impairment (see Section 4.2 Dose and Method of administration).

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

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.

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

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.

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. 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 not recommended. (see Section 4.3 Contraindications).

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.

Orthostatic hypotension has been reported in ambulatory patients administered Pethidine.

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

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

As opiate agonists may produce hyperglycaemia, this effect should be considered when diabetics require Pethidine.

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.

Use in Children:
Children up to 2 years of age may be more susceptible to the effects, especially the respiratory depressant effects of these drugs. Paradoxical excitation is especially likely to occur in paediatric patients receiving opioid analgesics.

Use in the Elderly:
Geriatric patients may be more susceptible to the effects, especially the respiratory depressant effects of the opioid analgesics. Also, geriatric patients are more likely to have prostatic hypertrophy or obstruction and age-related renal function impairment and are therefore more likely to be adversely affected by opioid-induced urinary retention. In addition, geriatric patients may metabolize or eliminate opioid analgesics more slowly than younger adults. Lower doses or longer dosing intervals than those usually recommended for adults may be required and are usually therapeutically effective for these patients.

Liver 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.

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.

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 Precautions section 4.4).

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

Monoamine oxidase inhibitors: Excitation, sweating, rigidity, hypertension or hypotension, coma have occurred with combination. Interaction with furazolidone is not likely until it has been taken for five days. Interaction with selegiline, a MAOI Type B, has been reported as causing delirium, restlessness, sweating and rigidity.

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 pethidine with other drugs that affect the serotonergic neurotransmitter system increases the risk of serotonin syndrome. Drugs that affect the serotonergic neurotransmitter system include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs).

4.6 Fertility, pregnancy and lactation

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 foetus (see also Pharmacology).

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

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

Use in Labour:
Opioid analgesics readily enter the foetal circulation when used during labour and may cause respiratory depression in the neonate, especially the premature neonate.

Use in 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 coordination, 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 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. Genito-urinary - Urinary retention and anuria.

Hepatic - Increased biliary tract pressure, choledochoduodenal sphincter spasm.

Nervous System - Pethidine associated neurotoxicity (see Special Warnings 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

Instructions to be Given to Patient

CNS depression is increased when Pethidine is co-administered with alcohol, butyrophenones, hypnotics, sedatives, phenothiazines, tricyclics, antihistamines and other CNS depressant agents.

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

Addictive Potential

Dependence on Pethidine may result after treatment with therapeutic doses. Use of Pethidine should therefore be restricted to short-term administration for the relief of severe pain not responding to non-opioid analgesics. Abrupt withdrawal of Pethidine in physically dependent individuals may precipitate acute withdrawal syndrome, including convulsions.

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://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

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 IV naloxone (e.g., 0.4 mg) 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 advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Actions
Pethidine, a phenylpiperidine derivative, is a synthetic opioid analgesic that acts mainly as a μ-opioid agonist. Pethidine is used for the relief of most types of moderate to severe acute pain including the pain of labour. It is more lipid soluble than morphine and has a less potent and shorter lasting analgesic effect: analgesia usually

lasts for 2 to 4 hours. Its short duration of action and accumulation of its potentially neurotoxic metabolite norpethidine on repeated dosage, make it unsuitable for the management of chronic pain. Pethidine has a weaker action on smooth muscle than morphine and its lower potential to increase biliary pressure may make it a more suitable opioid analgesic for pain associated with biliary colic and pancreatitis. It is also used for premedication and as an adjunct to anaesthesia. It has been given with phenothiazines such as promethazine to achieve basal narcosis. Pethidine has little effect on cough or on diarrhoea.

10 mg of morphine is equivalent in analgesic effect to approximately 100 mg of Pethidine.

5.2 Pharmacokinetic properties

Pethidine Hydrochloride is absorbed from the gastrointestinal tract, but only about 50% of the drug reaches the systemic circulation because of first-pass metabolism. Absorption after intramuscular injection is variable. Peak plasma concentrations have been reported 1 to 2 hours after oral doses. It is about 60 to 80% bound to plasma proteins.
Pethidine is metabolised in the liver, by hydrolysis to pethidinic acid (meperidinic acid) or demethylation to norpethidine (normeperidine) and hydrolysis to norpethidinic acid (normeperidinic acid), followed by partial conjugation with glucuronic acid. Norpethidine is pharmacologically active, and its accumulation may result in toxicity. Pethidine is reported to have a plasma elimination half-life of about 3 to 6 hours in healthy subjects; the metabolite norpethidine is eliminated more slowly, with a half-life reported to be up to about 20 hours. Both Pethidine and norpethidine appear in the CSF. At the usual values of urinary pH or if the urine is alkaline, only a small amount of Pethidine is excreted unchanged; urinary excretion of Pethidine and norpethidine is enhanced by acidification of the urine. Pethidine crosses the placenta and is distributed into breast milk.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to those included in other sections.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Acacia
Lactose monohydrate
Magnesium stearate
Maize starch

6.2 Incompatibilities

The mixing of thiopentone solutions with Pethidine results in the formation of a pharmacologically inactive complex. A loss of clarity of solution was noted when solutions of Pethidine hydrochloride were mixed with the following: aminophylline, heparin, amylobarbitone sodium, methicillin sodium, morphine sulphate, phenobarbitone sodium, phenytoin sodium, sodium bicarbonate or sodium iodide. Pethidine is also incompatible with alkalis, iodine and iodides.

6.3 Shelf life

36 months from date of manufacture when stored below 25°C

6.4 Special precautions for storage

Stored at or below 25°C protect from light and moisture. Store in original package. Keep out of reach of children.

6.5 Nature and contents of container

10's in glass bottles

6.6 Special precautions for disposal

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

7. MEDICINE SCHEDULE

Class B3 controlled drug

8. SPONSOR

Noumed Pharmaceuticals Limited
Auckland, New Zealand

Freephone 0800 527 545

9. DATE OF FIRST APPROVAL

31/12/1969

10. DATE OF REVISION OF THE TEXT

26/10/2023

SUMMARY TABLE OF CHANGES

Section changes	Summary of new information
Sponsor	Updated sponsor details.