PROFESSIONAL INFORMATION

SCHEDULING STATUS

S6

1 NAME OF THE MEDICINE

Pharma-Q Pethidine Injection 25 mg/1 ml solution for injection

Pharma-Q Pethidine Injection 50 mg/1 ml solution for injection

Pharma-Q Pethidine Injection 100 mg/2 ml solution for injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Pharma-Q Pethidine Injection 25 mg/1 ml:

1 ml ampoules containing 25 mg pethidine hydrochloride.

Pharma-Q Pethidine Injection 50 mg/1 ml:

1 ml ampoules containing 50 mg pethidine hydrochloride.

Pharma-Q Pethidine Injection 100 mg/2 ml:

2 ml ampoules containing 100 mg pethidine hydrochloride.

Sugar free.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless solution in clear, colourless glass ampoules.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Pharma-Q Pethidine Injection is indicated for the relief of severe pain.
- It is particularly useful for the relief of post-operative pain.
- It may be used to relieve labour pain.

4.2 Posology and method of administration

Posology

Children

Intramuscular injection

- 0,5 mg to 2 mg per kg body-mass, but not exceeding the adult dose.

Adults

Subcutaneous or Intramuscular injection

- 25 mg to 100 mg.

Slow intravenous injection

- In doses of 25 mg to 50 mg.

Obstetric analgesia

Intramuscular or subcutaneous injection

50 mg to 100 mg may be give as soon as contractions occur at regular intervals. This dose may be repeated after 1 to 3 hours if necessary.

Epidural administration

Slow injection

- Proper placement of needle or catheter in the epidural space should be verified before Pharma-Q Pethidine Injection is injected to assure that unintentional intravascular or intrathecal administration does not occur.
- Unintentional intrathecal injection of the full epidural doses could produce effects of high spinal anaesthesia including prolonged paralysis and delayed recovery.
- If analgesia is inadequate, the placement and integrity of the catheter should be verified prior to administration of any additional epidural medications.

- Pharma-Q Pethidine Injection should be administered by slow injection.
- With epidural administration, caution should be exercised in the presence of respiratory depression and in the presence of foetal distress.
- Epidural administration requires that the patient should be in a high care environment with continuous supervision.
- The patient should be closely monitored for at least 2 hours after each dose, as early respiratory depression may occur.

In addition to conventional routes of administration Pharma-Q Pethidine Injection may be given epidurally and intrathecally.
Intraspinal doses are in the region of 20 mg to 150 mg for initial epidural injection or at an infusion rate of 5 mg to 20 mg per hour. Onset of action is around 5 minutes. The duration of effect of a single dose is 4 to 8 hours.

Elderly or debilitated patients

The dosage should be reduced in elderly and debilitated patients.

Method of administration

Intramuscular, intravenous or subcutaneous injection.

4.3 Contraindications

Pharma-Q Pethidine Injection is contraindicated in

- Patients with a hypersensitivity to pethidine hydrochloride or to any of the excipients of Pethidine Pharma-Q Injection (see section 6.1).
- Patients who suffer from respiratory depression, especially in the presence of cyanosis and excessive bronchial secretion, chronic lung disease, renal and hepatic insufficiency.
- Patients who display a presence of acute alcoholism, convulsive disorder, head injuries,

and conditions in which intracranial pressure is raised.

- Patients who are being treated with monoamine oxidase inhibitors, or within 2 weeks of the discontinuation of such treatment (see section 4.5).
- Concomitant use with SSRIs, tramadol, St John's wort and triptans.
- Patients suffering from an attack of bronchial asthma or in heart failure secondary to chronic lung disease.
- Patients who are comatose.
- Use of Pharma-Q Pethidine Injection should be avoided in patients with supraventricular tachycardia.
- Pharma-Q Pethidine Injection should not be administered to patients receiving ritonavir.
- Use of Pharma-Q Pethidine Injection in patients with phaechromocytoma may result in hypertensive crisis.
- In patients with a risk of paralytic ileus.
- Pharma-Q Pethidine Injection should not be administered to patients with severe renal impairment or severe hepatic impairment.
- Use of Pharma-Q Pethidine Injection should be avoided in patients with diabetic acidosis where there is danger of coma.
- Patients who are pregnant or breastfeeding as safety has not been established (see section 4.6).

4.4 Special warnings and precautions for use

Prolonged use of Pharma-Q Pethidine Injection may lead to dependence of the morphine type.

Doses as large as 3 or 4 grams daily has been taken by addicts. As tolerance to the central nervous system stimulant and anticholinergic effects is not complete with these very large doses, muscle twitching, tremor, mental confusion, dilated pupils, and sometimes convulsions may be present.

The euphoric activity of pethidine and related medicines has led to their abuse.

Larger doses produce respiratory depression and hypotension, with circulatory failure and deepening coma. Convulsion may occur in infants and children. Death may occur from respiratory failure. Toxic doses vary considerably with the individual, with regular users tolerating large doses.

Local reactions often follow injection of pethidine due to the histamine-releasing effect. Intravenous injection may produce vasodilation and hypotension.

Contact dermatitis has been reported and pain and irritation may occur on injection.

Pharma-Q Pethidine Injection should be administered with caution or in reduced doses to patients with

- Hypothyroidism.
- Adrenocortical insufficiency.
- Acute or chronic airflow obstruction including asthma.
- Decreased respiratory reserve.
- History of convulsive disorder.
- Impaired kidney or liver function.
- Prostatic hyperplasia.
- Hypotension.
- Shock.
- Inflammatory or obstructive bowel disorders.
- Myasthenia gravis.
- Biliary tract disorders including those with pain secondary to gallbladder pathology.

Although less spasmogenic than morphine, pethidine may precipitate spasm of the ureter or Sphincter of Oddi.

Renal impairment may result in accumulation of the potentially toxic metabolite norpethidine, particularly with repeat dosing. All of these patient groups may experience increased or prolonged effects of the medicine.

It should be used in caution in patients with obstructive bowel disorders due to its effects on the gastrointestinal tract where it may precipitate toxic megacolon.

Pharma-Q Pethidine Injection has a slower elimination rate and a larger inter-subject variability in neonates and young infants compared to older children and adults, which may lead to dose related reactions such as respiratory depression. If pethidine use is contemplated in neonates or young infants (up to 12 months), any potential benefits of the drug need to be weighed against the relative risk to the patient.

Pharma-Q Pethidine Injection should be given with caution and in reduced doses, patients who are elderly or debilitated.

Pharma-Q Pethidine Injection should be used with caution in patients with existing hypotension as it may reduce the blood pressure further.

Risk from concomitant use of sedative medicines such as benzodiazepines or related medicines:

Concomitant use of pethidine and sedative medicines such as benzodiazepines or related medicines may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Pharma-Q Pethidine Injection concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible. The patients should be followed closely for signs and symptoms of respiratory depression and sedation.

In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5)

The administration of pethidine during labour may cause respiratory depression in the new born infant.

Mental health disorders

Pharma-Q Pethidine Injection should be used with particular care in patients with a personal or family history of substance abuse or mental health disorders including, but not limited to major depression, anxiety and alcohol and drug abuse.

Drug dependence, tolerance and potential for abuse

For all patients, prolonged use of Pharma-Q Pethidine Injection may lead to drug dependence (addiction), even at therapeutic doses. The risks are increased in individuals with current or past history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g., major depression).

Additional support and monitoring may be necessary when prescribing for patients at risk of opioid misuse.

A comprehensive patient history should be taken to document concomitant medications, including over the-counter medicines and medicines obtained on-line, and past and present medical and psychiatric conditions.

Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of pain control as initially experienced. Patients may also supplement their treatment with additional pain relievers. These could be signs that the patient is developing tolerance.

The risks of developing tolerance should be explained to the patient.

Overuse or misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else.

Patients should be closely monitored for signs of misuse, abuse, or addiction.

The clinical need for analgesic treatment should be reviewed regularly.

Drug withdrawal syndrome

Prior to starting treatment with any opioids, a discussion should be held with patients to put in place a withdrawal strategy for ending treatment with Pharma-Q Pethidine Injection.

Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take weeks to months.

The opioid drug withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.

If women use Pharma-Q Pethidine Injection during pregnancy, there is a risk that their newborn infants will experience neonatal withdrawal syndrome.

Hyperalgesia

Hyperalgesia may be diagnosed if the patient on long-term opioid therapy presents with increased pain.

This might be qualitatively and anatomically distinct from pain related to disease progression or to breakthrough pain resulting from development of opioid tolerance. Pain associated with hyperalgesia tends to be more diffuse than the pre-existing pain and less defined in quality. Symptoms of hyperalgesia may resolve with a reduction of opioid dose.

Paediatric population

Pethidine is not usually given pre-operatively to children under 1 year of age, and it should be given with extreme caution to newborn or premature infants for other conditions.

4.5 Interaction with other medicines and other forms of interaction

Antipsychotics

Concurrent administration of pethidine and phenothiazines produced severe hypotensive episodes and may prolong the respiratory depression due to pethidine.

Monoamine Oxidase Inhibitors

The concurrent use of MAOIs (including moclobemide) is contraindicated (see section 4.3) as they may result in CNS excitation or depression.

Very severe reactions, including coma, severe respiratory depression, cyanosis and hypotension have occurred in patients receiving monoamine oxidase inhibitors and given pethidine. There are also reports of hyperexcitability, convulsions, tachycardia, hyperpyrexia and hypotension (see section 4.3).

CNS depressants

The depressant effects pethidine are enhanced by depressants of the central nervous system such as alcohol, anaesthetics, hypnotics and sedatives, barbiturates, tricyclic antidepressants and phenothiazines.

Opioid agonists

Additive effects on CNS depression, respiratory depression and hypotension can occur with concomitant use of opioid agonist analgesics.

MAO-B inhibitors

Concomitant use of MAO-B inhibitors such as selegiline or rasagiline is contraindicated

(see section 4.3) as this may lead to hyperpyrexia and CNS toxicity.

Rasagiline should not be given with pethidine as there is risk of CNS toxicity, its use should be avoided for two weeks after taking rasagiline.

Anticonvulsants

Administration of phenytoin may cause an increase in hepatic metabolism of pethidine and subsequently increased levels of norpethidine (a toxic metabolite).

Anti-virals

Plasma concentrations of pethidine may be decreased by concomitant administration of ritonavir, however levels of norpethidine (a toxic metabolite) may rise. Concomitant administration of ritonavir and pethidine should be avoided (see section 4.3).

Histamine H_2 antagonists

Cimetidine can reduce the metabolism of pethidine resulting in increased plasma concentration. Cyclizine may counteract the haemodynamic benefits of opioids.

Effects of pethidine on other medicines

Pharma-Q Pethidine Injection may have an effect on the activities of other medicines, for example domperidone, as a consequence of reduced gastro-intestinal motility.

The plasma levels of ciprofloxacin may be reduced in the presence of opiate pre-medicants.

Plasma levels of mexiletine may also be reduced in the presence of opioid analgesics.

Possible increased serotonergic effects when pethidine is given with SSRI's.

Sedative medicines such as benzodiazepines or related medicines:

The concomitant use of opioids with sedative medicines such as benzodiazepines or related medicines increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use

should be limited (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy and lactation has not been established (see section 4.3).

The administration during labour may cause respiratory depression in the newborn infant. Respiratory depression varies according to the timing and size of the maternal dose. Foetal depression is not apparent immediately when delivery occurs and may occur 1-3 hours after delivery.

Breastfeeding

Pharma-Q Pethidine Injection crosses the placenta and is excreted in breast milk.

Patients should be advised to discontinue breastfeeding during treatment with Pharma-Q Pethidine Injection.

Fertility

There is no fertility data.

4.7 Effects on ability to drive and use machines

Pharma-Q Pethidine Injection may cause drowsiness that may affect the ability to perform skilled tasks. Patients who experience such effects should be advised not drive or operate machinery.

4.8 Undesirable effects

a. Summary of the safety profile

The frequency of adverse reactions reported with Pharma-Q Pethidine Injection are summarised in the table below according to system organ class.

b. Tabulated summary of adverse reactions

System organ class	Frequency	Adverse reactions
Immune system disorders	Frequency unknown	General hypersensitivity reactions
Psychiatric disorders	Frequency unknown	Dependence, confusion, changes of mood, mild euphoria, hallucinations, dysphoria
Nervous system disorders	Frequency unknown	Drowsiness, dizziness, tremor, convulsions, headache, fainting, CNS excitation, allodynia
Eye disorders	Frequency unknown	Dry eye, miosis, corneal reflex decreased
Ear and labyrinth disorders	Frequency unknown	Vertigo
Cardiac disorders	Frequency unknown	Tachycardia, bradycardia, palpitations
Vascular disorders	Frequency unknown	Orthostatic hypotension, flushing, hypotension, hypertension, vasodilation
Respiratory, thoracic and mediastinal disorders	Frequency unknown	Respiratory depression
Gastrointestinal disorders	Frequency unknown	Nausea, vomiting, constipation, dry mouth
Hepato-biliary disorders	Frequency unknown	Ureteric or biliary spasm

System organ class	Frequency	Adverse reactions
Skin and subcutaneous tissue disorders	Frequency unknown	Sweating, rash, urticaria, pruritus
Musculoskeletal and connective tissue disorders	Frequency unknown	Muscle twitching
Renal and urinary disorders	Less frequent	Difficulty in micturition, renal colic
Reproductive system and breast disorders	Frequency unknown	Sexual dysfunction
General disorders and administration site conditions	Less frequent	Drug withdrawal syndrome
	Frequency unknown	Hypothermia, weakness, injection site reactions including induration and irritation.

Post marketing experience

Increased risk of abdominal pain, including pancreatitis has been reported as a rare side effect.

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. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Symptoms and signs

Respiratory depression, CNS depression with extreme somnolence progressing to incoordination, stupor or coma, convulsions, CNS stimulation, cyanosis, miosis, skeletal muscle flaccidity or tremors, cold, clammy skin, hypothermia, bradycardia and hypotension. In severe overdosage, apnoea, circulatory collapse, pulmonary oedema, mydriasis, cardiac arrest and death may occur.

After overdosage, symptoms are generally similar to those of morphine poisoning, however, stimulation of the central nervous system and convulsions may also occur, especially in tolerant individuals or following toxic doses by mouth.

Management of overdose

Intensive supportive therapy may be required to correct respiratory failure and shock.

A patent airway must be established with assisted or controlled ventilation. If signs of CNS toxicity are exhibited the use of pethidine should be discontinued.

In addition, the specific antagonist naloxone hydrochloride is used to counteract very rapidly the severe respiratory depression and coma produced by excessive doses of pethidine.

In adults a dose of 0,4 mg to 2 mg is given intravenously, repeated at interval of 2 to 3 minutes if necessary, up to 10 mg.

In children a dose of 10 mcg/kg body-mass intravenously initially is given. If necessary, followed by a larger dose of 100 mcg/kg.

Naloxone may also be given by subcutaneous or intramuscular injection.

The effect of naloxone may be of shorter duration than that of the opioid analgesic and additional doses may be required to prevent relapses.

The use of opioid antagonists such as naloxone, nalorphine, and levallorphan in persons physically dependant on pethidine or related agents may induce withdrawal symptoms.

Anti-convulsive therapy, oxygen, intravenous fluids, vasopressors and other supportive measures should be employed.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 2.9 Other Analgesics.

Pharmacotherapeutic group: Analgesics – Phenylpiperidine derivatives.

ATC code: NO2A B.

Pethidine hydrochloride is predominantly a mu (μ) receptor agonist similar to morphine although less potent and shorter acting, and it exerts its chief pharmacological actions on the central nervous system, the neural elements in the

bowel and smooth muscles via the peripheral nervous system. However, it has a weaker action on smooth muscle than morphine and therefore has less effect on cough, bowel motility, biliary tone and secretion of pituitary hormones. Pethidine also causes the release of histamine from mast cells resulting in a number of allergic-type reactions.

Analgesia:

The onset of analgesic effect is within 10 minutes, after subcutaneous or intramuscular administration and reaches a peak in about 1 hour that corresponds closely to peak concentrations in plasma. In clinical use, the duration of effective analgesia is approximately 3 to 5 hours.

In general, 75 to 100 mg of Pethidine given parenterally is approximately equivalent to 10 mg of morphine.

Other central nervous systems actions:

Peak respiratory depression is observed within 1 hour after intramuscular administration, and there is a return toward normal values at about 2 hours, although minute volume is usually measurably depressed for as long as 4 hours.

Pethidine is a narcotic analgesic with similar actions to morphine.

5.2 Pharmacokinetic properties

Absorption

Pethidine is rapidly absorbed following intramuscular or subcutaneous injection, however, there are wide inter-individual variations.

Distribution

It is widely distributed in the tissues with a volume of distribution of 200-300 litres and is extensively protein bound (60-80 %).

Biotransformation

Pethidine is metabolised in the liver and excreted via the urine (70 % in 24 hours). One of the metabolites, norpethidine, is pharmacologically active and its accumulation can result in toxicity.

Elimination

Urinary excretion is pH-dependent, the lower the pH the greater the clearance. At normal urinary pH only a small amount of pethidine is excreted unchanged.

Pethidine has a plasma elimination half-life of about 3 to 6 hours. The metabolite norpethidine is eliminated more slowly with a half-life of up to 20 hours and may accumulate with chronic use, especially in the presence of renal impairment. Pethidine crosses the placenta and is excreted in breast milk.

Both pethidine and norpethidine cross the blood/brain barrier and are found in the cerebrospinal fluid.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid (to adjust pH)

Water for injections

6.2 Incompatibilities

Pharma-Q Pethidine Injection is incompatible with barbiturate salts and with other

medicines including aminophylline, heparin sodium, methicillin sodium, morphine sulphate, nitrofurantoin sodium, phenytoin sodium, sulphadiazine sodium, sodium iodide, sulphafurazole diethanolamine. Incompatibility has also been observed between pethidine hydrochloride and acyclovir sodium, imipenem, frusemide and idarubicin.

Colour changes or precipitation have been observed on mixing pethidine with the following medicines, minocycline hydrochloride, tetracycline hydrochloride, cefoperazone sodium, mezlocillin sodium, nafcillin sodium and liposomal doxorubicin hydrochloride.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 ºC.

Protect from light.

6.5 Nature and contents of container

Pharma-Q Pethidine Injection 25 mg/1 ml: Containers of 10 or 100 x 1 ml ampoules

Pharma-Q Pethidine Injection 50 mg/1 ml: Containers of 10 or 100 x 1 ml ampoules

Pharma-Q Pethidine Injection 100 mg/2 ml: Containers of 10 or 100 x 2 ml ampoules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

PHARMA-Q HOLDINGS (PTY) LTD

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8 REGISTRATION NUMBERS

Pharma-Q Pethidine Injection 25 mg/1 ml: 31/2.9/0083

Pharma-Q Pethidine Injection 50 mg/1 ml: 31/2.9/0084

Pharma-Q Pethidine Injection 100 mg/2 ml: 31/2.9/0085

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Original date of registration: 04 December 1996

10 DATE OF REVISION OF THE TEXT

07 July 2026