Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Pethidine Hydrochloride 50mg/ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1ml of solution contains 50mg of Pethidine Hydrochloride.
Each 2ml of solution contains 100mg of Pethidine Hydrochloride.

Excipient with known effect
None

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection (Injection)
A clear colourless, sterile solution for injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

As an analgesic in the relief of moderate to severe pain.
As an adjunct in anaesthesia.
For preoperative medication
During labour

4.2 Posology and method of administration

Posology

Adults
The usual dose is 25 to 100mg intramuscularly or subcutaneously or 25 to 50mg by slow intravenous injection. Dosage may be repeated if required every 4 hours.

Elderly or debilitated patients
In view of their greater sensitivity, the initial dose should not exceed 25mg.

Paediatricpopulation
The usual dose is 0.5 to 2mg/kg body weight. Dosage may be repeated if required every 4 hours.
The use of a small graduated syringe is recommended for the accurate administration of dosages given to children. In the absence of graduated syringes, the solution should be diluted with Water for Injections before measuring the dose.

Method of administration

Pethidine Hydrochloride 50mg/ml Solution for Injection is for administration by subcutaneous, intramuscular or slow intravenous injection.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Use of pethidine should be avoided in patients with diabetic acidosis where there is danger of coma
- In comatose patients
- Use of pethidine in patients with Phaeochromocytoma may result in hypertensive crisis.

- Use in patients who are receiving, or have within two weeks received, monoamine oxidase inhibitors (including moclobemide, and the monoamine B inhibitors selegiline and rasagiline).

- Use in patients with acute respiratory depression, severe obstructive airways disease or acute asthma and when there is risk of paralytic ileus or obstructive airways disease.
- It should not be administered to patients with severe renal impairment or severe hepatic impairment.
- Should be avoided in patients with acute alcoholism, delirium tremens, raised intracranial pressure, in head injury or in those with convulsive states such as status epilepticus.
- Pethidine should not be administered to patients receiving ritonavir.
- Use of pethidine should be avoided in patients with supraventricular tachycardia.

4.4 Special warnings and precautions for use

Repeated use may result in dependence of the morphine type.

Pethidine should be used with caution or in reduced doses in patients with myasthenia gravis.

Pethidine should be used with extreme caution and in reduced dosage in neonates, premature infants, patients who are elderly or debilitated or those with impaired hepatic or renal function. 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 product.

Pethidine should be used with caution in the elderly, the debilitated, or patients with hypothyroidism, adrenocortical insufficiency, shock, liver dysfunction, renal insufficiency or history of convulsive disorders.

Although less spasmogenic than morphine, pethidine may precipitate spasm of the ureter or Sphincter of Oddi. Subsequently it should be used with caution in patients with prostatic hypertrophy and biliary tract disorders including those with pain secondary to gallbladder pathology.

Repeated use will induce physical and psychological dependence, with a withdrawal
syndrome on cessation of therapy.
Excessive dosage (relative or absolute) may induce convulsions.
Pethidine should only be administered with great caution to patients with supraventricular tachycardia, respiratory dysfunction, increased intracranial pressure, acute alcoholism.

Repeated use will result in the development of tolerance and cross tolerance with other narcotic analgesics, requiring increases in dosage to achieve the required effect.
If the intravenous route is being used, Pethidine should be given slowly in order to reduce the risk of adverse reactions.

Use of Pethidine in prolonged increasing dosage or concomitantly with anticholinergics may result in neurotoxicity in patients with renal failure, cancer or sickle cell anaemia and that severe hypotension may occur when Pethidine is administered to patients whose ability to maintain blood pressure has been compromised by a depleted blood volume by the administration of drugs such as phenothiazines.

In addition, it should be avoided in patients and with obstructive or inflammatory bowel disorders due to its effects on the gastrointestinal tract where it may precipitate toxic megacolon.

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs:
Concomitant use of Pethidine and sedative medicines such as benzodiazepines or related drugs 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 Pethidine 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).

<u>Paediatric population</u>

Pethidine 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.

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Monoamine Oxidase Inhibitors
The concurrent use of MAOIs (including moclobemide) is contra-indicated (see section 4.3) as they may result in CNS excitation or depression.
Very severe reactions including coma, respiratory depression, cyanosis and hypotension have occurred in patients administered monoamine oxidase inhibitors (MAOIs). Pethidine should not be administered to patients taking MAOIs or to those who have taken MAOIs within 14 days (see section 4.3).The interaction of pethidine with MAOIs may result in Serotonin syndrome.

CNS depressants
The central depressant effects of pethidine may be potentiated by the concurrent use of other central nervous system depressants including sedatives, phenothiazine neuroleptics, anxiolytics, antidepressants, other analgesics, alcohol and general anesthetics; respiratory depression, hypotension or profound sedation or coma may result.

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).

Antipsychotics
Concomitant use of phenothiazines and pethidine can induce severe hypotension.

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 H2 antagonists
Cimetidine inhibits metabolism of pethidine and therefore increases plasma concentration.

Effects of pethidine on other drugs
Pethidine may have an effect on the activities of other drugs, for example domperidone, as a consequence of reduced gastro-intestinal motility.
The plasma levels of ciprofloxacin may be reduced in the presence of opiate premedicants.
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 drugs:
The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs 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

Pethidine should not be administered in pregnancy prior to the period of labour, unless the potential benefits outweigh the possible hazards, because the safe use of Pethidine in pregnancy prior to labour has not been established relative to possible adverse effects on foetal development.
There is inadequate evidence of safety in human pregnancy, but the drug has been in widely use for many years without apparent ill consequence. Animal studies have not shown any hazard. Administration during labour may cause respiratory depression in the newborn.

Breast-feeding
All the narcotic analgesics are able to traverse the placenta and are excreted in milk. This should be borne in mind when considering their use in patients during pregnancy or lactation.

Fertility
No data available

4.7 Effects on ability to drive and use machines

The product will cause drowsiness and reduce alertness. Patients should be advised not to operate machinery until the effects on physical and mental ability have gone.

The ability to drive or use machines may be severely affected during and for some time after administration of pethidine.This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:

- The medicine has been prescribed to treat a medical or dental problem and
- You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
- It was not affecting your ability to drive safely

4.8 Undesirable effects

The information below lists reported adverse reactions, ranked using the following frequency classification:

Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

System Organ Class	Frequency	Adverse Event
Immune system disorders	Not known	General hypersensitivity reactions
Psychiatric disorders	Not known	Dependence, confusion, mood altered, mild euphoria, hallucinations, dysphoria, agitation, anxiety, nervousness.
Nervous system disorders	Very common	Drowsiness, dizziness, tremor, convulsions, headache, CNS excitation, syncope, lightheadedness, sedation, uncoordinated muscle movements
Eye disorders	Not known	Visual disturbances, dry eye, miosis
Ear and labyrinth disorders	Not known	Vertigo
Cardiac disorders	Not known	Tachycardia, bradycardia, palpitations
Vascular disorders	Very common	Flushing of face, orthostatic hypotension, hypotension, hypertension, vasodilatation
Respiratory, thoracic and mediastinal disorders	Very common	Respiratory depression
Gastrointestinal disorders	Very common	Nausea, vomiting, dry mouth, constipation

Hepatobiliary disorders	Not known	Biliary or Ureteric spasm
Skin & subcutaneous tissue disorders	Very common	Sweating, other skin rash, urticaria, pruritis
Musculoskeletal and connective tissue disorders	Not known	Muscle twitching
Renal & urinary disorders	Not known	Difficulty in micturition, renal colic, urinary retention
Reproductive system and breast disorders	Not known	Sexual dysfunction
General disorders & administration site conditions	Not known	Hypothermia, weakness, injection site reaction including induration and irritation, pain at the injection, wheal and flare over the vein with intravenous injection, local tissue irritation
Investigations	Not known	Corneal reflex decreased

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

Symptoms

Respiratory depression, CNS depression with extreme somnolence progressing to in coordination, 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.

Management

Intensive supportive therapy may be required to correct respiratory failure and shock. A patent airway must be maintained and assisted respiration may be required. If signs of CNS toxicity are exhibited the use of pethidine should be discontinued.
Narcotic antagonists may be required if there is evidence of significant respiratory or cardiovascular depression.
The specific narcotic antagonist naloxone hydrochloride is used to counteract respiratory depression and coma. A dose of 0.4 to 2mg is given intravenously and may be repeated at intervals of 2 to 3 minutes if necessary, up to 10mg.
An anticonvulsant drug may be required to control seizures. Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics – Phenylpiperidine derivatives, ATC Code**:** N02AB02

Mechanism of action
Pethidine is a synthetic opioid analgesic similar to morphine although less potent and shorter acting. Its analgesic effect usually lasts for 2 to 4 hours. The analgesic effect occurs after about 10 minutes following parenteral administration. It acts on the CNS system 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.

Pharmacodynamic effects
Like other opioids, Pethidine binds to opioid receptors and exerts its principal pharmacological actions on the central nervous system where its analgesic and sedative effects are of particular therapeutic value.

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 interindividual 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%) with peak effects at 15-120 minutes, depending on the route of administration

Biotransformation and Elimination
The drug is metabolized in the liver and metabolites excreted mainly via urine (70% in 24 hours), with a T1/2 of 3-6 hours. Norpethidine, one of the metabolites, has a greater excitatory but fewer depressant effects on patients than Pethidine. Its accumulation may result in toxicity. 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. 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.

Paediatric population
A single study of pethidine pharmacokinetics was conducted in 21 infant patients who received a single 1mg/kg dose following surgery or during mechanical ventilation. V_c, V_{ss} and $t_{1/2}$ was shown to vary greatly between infant subjects, but were not demonstrated to correlate with age, gestational age, postconceptional age, weight or body surface area. Clearance was demonstrated to correlate with age, gestational age, postconceptional age, weight and body surface area. Median elimination half-life was demonstrated to be 10.7 hours (range 3.3. to 59.4 hours), median clearance was 8.0 ml/kg/min (range 1.8 to 34.9 ml/kg/min), median volume of the central compartment 2.4 L/kg (range 0.5 to 4.8 L/kg) and median steady-state volume of distribution was 7.2 L/kg (range 3.3 to 11.0 L/kg).

5.3 Preclinical safety data

No further relevant information other than that which is included in other sections of the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide
or
Dilute Hydrochloric acid (for pH adjustment)
Water for injections

6.2 Incompatibilities

There was loss of clarity when intravenous solutions of Pethidine hydrochloride were mixed with those of aminophylline, amylobarbitone sodium, heparin sodium, methicillin sodium, morphine sulphate, nitrofurantoin sodium, pentobarbitone sodium, phenobarbitone sodium, phenytoin sodium, sodium bicarbonate, sodium iodide, sulphadiazine sodium, sulphafurazole, diethanolamine or thiopentone sodium.

6.3 Shelf life

Unopened: 4 years
Once opened: use immediately

6.4 Special precautions for storage

Do not store above 25°C.
Keep ampoule in the outer carton in order to protect from light.

6.5 Nature and contents of container

1 ml and 2 ml, clear glass one-point-cut (OPC) ampoules, glass type I Ph. Eur. borosilicate glass, packed in cardboard cartons to contain 10 x 1 ml or 10 x 2 ml ampoules.

6.6 Special precautions for disposal

For single use only.
If only part of the contents of an ampoule is used, the remaining solution should be discarded.

7 MARKETING AUTHORISATION HOLDER

Mercury Pharmaceuticals (Ireland) Ltd
4045 Kingswood Road
Citywest Business Park
Co Dublin
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0073/014/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1st April 1978

Date of last renewal: 1st April 2008

10 DATE OF REVISION OF THE TEXT

October 2022