1.4.1. PRESCRIBING INFORMATION (SUMMARY OF PRODUCTS CHARACTERISTICS)

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

VERPAT (Pethidine Hydrochloride Injection BP 100mg/2ml)

2. Qualitative and Quantitative composition

2.1 Qualitative composition

Each ml contains

Pethidine Hydrochloride BP

Water for Injection BP

2.2 Quantitative composition

Each ml contains

Pethidine Hydrochloride BP 50mg

Water for Injection BP qs

For the full list of excipients, see section 6.1

2.3 Salts and hydrates

Pethidine Hydrochloride is equivalent to 100mg of Pethidine.

2.4 Esters and pro-drugs

Not Applicable

2.5 Oral powders for solution or suspension

Not Applicable

2.6 Parenteral excluding powders for reconstitution

Each ml contains

Pethidine Hydrochloride BP 50mg

2.7 Powders for reconstitution prior to parenteral administration

Not Applicable

2.8 Concentrates

Not Applicable

2.9 Transdermal patches

Not Applicable

2.10 Multi dose solid or semi-solid products

Not Applicable

2.11 Biological medicinal products

2.11.1 Expression of strength

Not Applicable

2.11.2 The biological origin of the active substance

Not Applicable

2.11.3 Special provisions for normal immunoglobulins

Not Applicable

2.11.4 Herbal pharmaceutical products

Not Applicable

3. Pharmaceutical form

Solution for Injection

A clear colourless, solution

4. Clinical particulars

4.1 Therapeutic indications

Relief of moderate to severe pain.

Premedication.

Obstetric analgesia.

Enhancement of analgesia

4.2 Posology and method of administration

Posology

Adults

For moderate or severe pain.

Normal single dose (usually not to be repeated more often than 4 hourly)

By intramuscular or subcutaneous injection	25 - 100 mg.
By slow intravenous injection	25 - 50 mg.

For obstetric analgesia.

By intramuscular or subcutaneous injection repeated 1 - 3 hours later. 50 - 100 mg.

Maximum of 400mg in 24 hours.

As a premedication.

By intramuscular injection one hour prior to the operation. 50 - 100mg

For the enhancement of analgesia.

By slow intravenous injection. 10 - 25mg as required.

Elderly or debilitated patients.

Initial doses should not exceed 25mg as this group of patients may be specially sensitive to the central depressant effect of the drug.

Paediatric population

For moderate or severe pain.

By intramuscular injection. 0.5 - 2 mg per Kg of body weight.

As a premedication.

By intramuscular injection one hour prior to the operation. 1 - 2 mg per kg of body weight.

4.3 Method of administration

Intramuscular, intravenous or subcutaneous injection

4.4 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1

Severe respiratory depression, severe obstructive airways disease or acute asthma.

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 or in those with convulsive states such as status epilepticus.

It should not be administered to patients receiving monoamine oxidase inhibitors (including moclobemide, and the monoamine B inhibitors selegiline and rasagiline) or within two weeks of their withdrawal.

Pethidine should not be administered to patients receiving ritonavir.

Use of pethidine should be avoided in patients with supraventricular tachycardia.

Use of pethidine in patients with phaechromocytoma may result in hypertensive crisis.

Use of pethidine should be avoided in patients with diabetic acidosis where there is danger of coma.

In comatose patients

In patients with a risk of paralytic ileus

In patients with head injuries.

4.5 Special warnings and precautions for use

Pethidine is controlled under the Misuse of Drugs Act 1971 (Schedule 2).

Repeated use may result in dependence of the morphine type.

Pethidine should be used with caution in patients with acute or chronic airflow obstruction including asthma.

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

Pethidine should only be given with caution and in reduced doses to 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 patients with shock, hypothyroidism, adreno-corticol insufficiency and a 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.

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

In addition it should be avoided in patients with severe inflammatory bowel disease 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).

4.6 Paediatric population

For moderate or severe pain.

By intramuscular injection. 0.5 - 2 mg per Kg of body weight.

As a premedication.

By intramuscular injection one hour prior to the operation. 1 - 2 mg per kg of body weight.

4.7 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.

Pethidine should not be administered to patients receiving monoamine oxidase inhibitors or moclobemide or within two weeks of their withdrawal (see Section 4.3).

CNS depressants

CNS depressants such as alcohol, hypnotics, anxiolytics and sedatives, barbiturates and tricyclic antidepressants may increase the general depressant effects of pethidine and should therefore be used with caution.

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 can reduce the metabolism of pethidine resulting in increased 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).

4.8 Additional information on special populations

4.9 Paediatric population

For moderate or severe pain.

By intramuscular injection. 0.5 - 2 mg per Kg of body weight.

As a premedication.

By intramuscular injection one hour prior to the operation. 1 - 2 mg per kg of body weight.

4.10 Fertility, pregnancy and lactation

4.10.1 Pregnancy

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.

As with all drugs during pregnancy care should be taken in assessing the risk to benefit ratio. Administration during labour may cause respiratory depression in the new-born infant.

4.10.2 Lactation:

Pethidine crosses the placental barrier and is excreted in breast milk. Patients should be advised to discontinue breast-feeding during treatment with pethidine

4.11 Effects on ability to drive and use machines

Patients should not drive or use machines while taking pethidine as it may cause drowsiness and reduce alertness.

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

4.12 Undesirable effects

There are no modern clinical studies available that can be used to determine the frequency of undesirable effects. Therefore, all the undesirable effects listed are classified as "frequency unknown" (cannot be estimated from the available data).

The undesirable effects listed below include class effects for opioid analgesics and effects related to the pharmacologically active metabolite, norpethidine.

System Organ Class	Frequency	Adverse Event
Immune system disorders	Unknown	General hypersensitivity reactions
Psychiatric disorders	Unknown	Dependence, confusion, mood altered, mild euphoria, hallucinations, dysphoria

Nervous system disorders	Unknown	Drowsiness, dizziness, tremor, convulsions, headache, fainting, CNS excitation
Eye disorders	Unknown	Dry eye, miosis, corneal reflex decreased
Ear and labyrinth disorders	Unknown	Vertigo
Cardiac disorders	Unknown	Tachycardia, bradycardia, palpitations
Vascular disorders	Unknown	Orthostatic hypotension, flushing, hypotension, hypertension, vasodilation
Respiratory, thoracic and mediastinal disorders	Unknown	Respiratory depression
Gastrointestinal disorders	Unknown	Nausea, vomiting, dry mouth, constipation
Hepatobiliary disorders	Unknown	Biliary or Ureteric spasm
Skin & subcutaneous tissue disorders	Unknown	Sweating, rash, urticaria, pruritus
Musculoskeletal and connective tissue disorders	Unknown	Muscle twitching
Renal & urinary disorders	Unknown	Difficulty in micturition, renal colic
Reproductive system and breast disorders	Unknown	Sexual dysfunction
General disorders & administration site conditions	Unknown	Hypothermia, weakness, injection site reactions including induration and irritation

4.13 Overdose

Symptoms

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.

Management

Treatment is supportive. 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. Narcotic antagonists may be required if there is evidence of significant respiratory or cardiovascular depression.

Naloxone should be given intravenously as soon as possible and repeated every 2-3 minutes if necessary (refer to naloxone product literature for details).

Anti-convulsive therapy, 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: NO2A B.

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.

Pethidine is a narcotic analgesic with similar actions to morphine.

5.2 Pharmacokinetic properties

Pethidine is rapidly absorbed following intramuscular or subcutaneous injection, however, there are wide inter-individual variations. It is widely distributed in the tissues with a volume of distribution of 200-300 litres and is extensively protein bound (60-80%).

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.

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.

5.3 Preclinical safety data

No additional pre-clinical data of relevance to the prescriber.

6. Pharmaceutical particulars

6.1 List of excipients

Sodium Hydroxide.

Water for Injection

6.2 Incompatibilities

In the absence of incompatibility studies, Pethidine must not be mixed with other medicinal products.

Pethidine is incompatible with barbiturate salts and with other drugs 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 drugs, 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 a temperature not exceeding 30°C. Protect from light.

6.5 Nature and contents of container

2ml in clear glass ampoules. Packed in cartons of 10x10x2 ml ampoules.

6.6 Special precautions for disposal and other handling

Pethidine is controlled under the Misuse of Drugs Act 1971 (Schedule 2).

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESSES

Marketing Authorisation Holder

Verve Human Care Laboratories
15-A, Pharmacity,
Selaqui, Dehradun-248011
India

Manufacturing Site:

Verve Human Care Laboratories
15-A, Pharmacity,
Selaqui, Dehradun-248011
India

8. MARKETING AUTHORISATION NUMBER

Not Applicable

9. DATE OF FIRST REGISTRATION/RENEWAL OF THE REGISTRATION

Not Applicable

10. DATE OF REVISION OF THE TEXT

11. DOSIMETRY (IF APPLICABLE)

Not Applicable

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

Not Applicable