**Summary of Product Characteristics**

## 1. Name of the medicinal product:

Petherol – Pethidine Hydrochloride 50mg in 1ml & 100mg in 2ml Solution for Injection

## 2. Qualitative and quantitative composition

Each 50mg ampoule contains 50mg of Pethidine Hydrochloride in 1ml of solution. Each 100mg ampoule contains 100mg of Pethidine Hydrochloride in 2ml of solution.
For a full list of excipients, see section 6.1.

## 3. Pharmaceutical form

Solution for injection

## 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 25mg - 100mg. By slow intravenous injection 25mg - 50mg.
For obstetric analgesia.
By intramuscular or subcutaneous injection repeated 1-3 hours later. 50mg - 100mg. Maximum of 400mg in 24 hours.
As a premedication.
By intramuscular injection one hour prior to the operation. 50mg - 100mg
For the enhancement of analgesia.
By slow intravenous injection. 10mg - 25mg as required.
Elderly or debilitated patients.
Initial doses should not exceed 25mg as this group of patients may be especially sensitive to the central depressant effect of the drug.
Paediatric population
For moderate or severe pain.
By intramuscular injection. 0.5mg-2mg per Kg of body weight.
As a premedication.
By intramuscular injection one hour prior to the operation. 1mg-2mg per kg of body weight.

**Method of administration**

Intramuscular, intravenous or subcutaneous injection

## 4.3 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 phaeochromocytoma 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.

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    - In patients with head injuries.

## 4.4 Special warnings and precautions for use

Pethidine is a controlled drug.
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-cortical 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).

## 4.5 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. 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.

*Antivirals*

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 premedication.
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**

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.

**Lactation**

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

## 4.7 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.

## 4.8 Undesirable effects

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

**Tabulated summary of adverse reactions**

Adverse reactions reported in the following table by MedDRA System Organ Class (SOC), Preferred Term and frequency. The following frequency categories are used:

| Term | Frequency of occurrence |
|---|---|
| Very common | (≥1/10) |
| Common | (≥1/100 to <1/10) |
| Uncommon | |
| 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 | Undesirable effects |
|---|---|---|
| **Immune System Disorders** | Not Known | General hypersensitivity reactions. |
| **Psychiatric Disorders** | Not Known | Dependence, confusion, mood altered, mild euphoria, hallucinations, dysphoria. |
| **Nervous system disorders** | Not Known | Drowsiness, dizziness, tremor, convulsions, headache, fainting, CNS excitation. |
| **Eye Disorders** | Not Known | Dry eye, miosis, corneal reflex decreased |
| **Ear and labyrinth Disorders** | Not Known | Vertigo |
| **Cardiac Disorders** | Not Known | Tachycardia, bradycardia, palpitations |
| **Vascular disorders** | Not Known | Orthostatic hypotension, flushing, hypotension, hypertension, vasodilation |
| **Respiratory, Thoracic and Mediastinal Disorders** | Not Known | Respiratory depression |
| **Gastro-intestinal disorders** | Not Known | Nausea, vomiting, dry mouth, constipation |
| **Hepatobiliary Disorders** | Not Known | Biliary or Ureteric spasm |
| **Skin and Subcutaneous Tissue Disorders** | Not Known | Sweating, rash, urticaria, pruritus |
| **Musculoskeletal and Connective Tissue Disorders** | Not Known | Muscle twitching |
| **Renal and Urinary Disorders** | Not Known | Difficulty in micturition, renal colic. |
| **Reproductive System and Breast Disorders** | Not Known | Sexual dysfunction |

| | | |
|---|---|---|
| **General Disorders and Administration Site Condition** | Not Known | Hypothermia, weakness, injection site reactions including induration and irritation |

## 4.9 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**
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injections

**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**
Unopened: 24 Months
After opening: The product must be used immediately.

**6.4 Special precautions for storage:**
Do not store above 30°C. Keep the container in the outer carton to protect from light. Do not use if particulate matter is present.

**6.5 Nature and contents of container**
Clear glass ampoules, glass type I, Ph. Eur. Pack sizes (50mg): 10 x 1ml
Pack sizes (100mg): 10 x 2ml

**6.6 Special precautions for disposal and other handling:**
Pethidine is a controlled drug.
For single use only. Discard any unused contents.
Any unused medicinal product or waste material should be disposed of in accordance with local requirement

**7. Marketing authorization holder and manufacturing site addresses**

**Marketing authorization holder:**

Company) Name: Tasa Pharma Ltd
Address: Unit C1-C3, Kay Complex, Mombasa Road, Nairobi, P.O. Box 3959-00506 Country: Kenya
Telephone: +254(0)207650833:
E-Mail: hitesh@tasapharma.com

**Manufacturing site address:**

Company) Name: Tasa Pharma Ltd
Address: Unit C1-C3, Kay Complex, Mombasa Road, Nairobi, P.O. Box 3959-00506 Country: Kenya
Telephone: +254(0)207650833
E-Mail: hitesh@tasapharma.com

**8. Marketing authorization number**

CTD9935

**9. Date of first registration**

13/12/2022

**10. Date of revision of the text:**

13/09/2023

**11. Dosimetry:**

Not Applicable

**12. Instructions for Preparation of Radiopharmaceuticals:**

Not Applicable