SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Pethidine Injection BP

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Pethidine Hydrochloride 50mg/ml

3 PHARMACEUTICAL FORM

Solution for Injection

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Pethidine hydrochloride may be used in the management of severe pain, including pain associated with surgical procedures, as a pre-anaesthetic medication and in obstetric analgesia.

4.2 Posology and method of administration

Pethidine may be given by intramuscular, subcutaneous or slow intravenous injection. For intravenous administration the contents of the ampoule can be diluted to 10ml with Water for Injections giving a strength of 5 mg/ml(1 ml ampoule) or 10 mg/ml (2ml ampoule).

Pre-anaesthetic medication

Administered about one hour before the operation.

Adults : 5*0*mg-100mg by intramuscular injection.

Elderly: 50mg-100mg by intramuscular injection.

Elderly patients may be more sensitive to pethidine.

Children: 1.0 to 2.0mg/kg by intramuscular injection

Obstetric analgesia

50-100mg may be given by intramuscular or subcutaneous injection as soon as contractions occur at regular intervals. The dose may be repeated after one to three hours if necessary up to a maximum of 400mg in 24 hours.

Management of severe pain, including post-operative pain

Adults : 25 mg-100mg by intramuscular or subcutaneous injection every four hours

By slow intravenous injection 25-50mg repeated every four hours.

Elderly: 25 mg-100mg by intramuscular or subcutaneous injection every four hours.

By slow intravenous injection 25-50mg repeated every four hours.

Elderly patients may be more sensitive to pethidine. The total daily dose may need to be reduced in elderly patients receiving repeated doses. Initial doses should not exceed 25mg as this group of patients may be especially sensitive to the central depressant effect of the drug.

Children 0.5 - 2mg/kg by intramuscular injection every four hours.

Hepatic impairment

The dose should be reduced.

Renal impairment

The dose should be reduced in mild to moderate impairment. Severe renal impairment is a contraindication to use (see 4.3 Contraindications).

For concomitant illnesses/conditions where dose reduction may be appropriate see 4.4 Special Warnings and Precautions for Use

4.3 Contraindications

- Known hypersensitivity to pethidine.
- Severe renal impairment.
- Acute respiratory depression.
- Concurrent use of monoamine oxidase inhibitors (including moclobemide and phenelzine) or use within two weeks of their discontinuation, as severe CNS excitation or depression (hypertension or hypotension) may occur.
- Concurrent use of ritonavir – risk of norpethidine toxicity.
- Concurrent use of selegiline – risk of hyperpyrexia and CNS toxicity.
- Phaeochromocytoma
- Coma
- Raised intracranial pressure or head injury, as there is an increased risk of respiratory depression that may lead to elevation of CSF pressure. The sedation and pupillary changes produced may interfere with accurate monitoring of the patient.
- Acute alcoholism.
- Where there is a risk of paralytic ileus or in acute diarrhoeal conditions associated with antibiotic-induced pseudomembranous colitis or diarrhoea caused by poisoning (until the toxic material has been eliminated).

4.4 Special warnings and precautions for use

Repeated administration of pethidine may lead to dependence and tolerance developing, but this should not deter its use in the control of pain in terminal illness. Abrupt withdrawal in patients who have developed tolerance may precipitate a withdrawal syndrome. Caution should be exercised in patients with a known tendency or history of drug abuse. Babies born to opioid dependent mothers may suffer withdrawal symptoms.

Use with caution or reduce the dosage in asthma and decreased respiratory reserve (including kyphoscoliosis, emphysema, severe obesity, cor pulmonale); avoid use during an acute asthma attack (see also 4.3 Contraindications).

Use with caution or in reduced doses in patients with biliary tract disorders, hypothyroidism, adreno-cortical insufficiency, hypotension, shock, prostatic hypertrophy, urethral stricture, inflammatory or obstructive bowel disorders, myasthenia gravis, supraventricular tachycardia, a history of convulsive disorders, and in debilitated patients.

Pethidine neurotoxicity may be seen in patients with renal failure, cancer or sickle cell anaemia, during concomitant administration of drugs that may increase the production of the metabolite norpethidine (see 4.5 Interactions) or during prolonged administration of increasing pethidine doses.

Renal impairment: severe impairment, see 4.3 Contraindications; mild to moderate renal impairment, dosage reduction recommended (see 4.2 Posology).

Care should be exercised in treating infants, elderly patients and those with hepatic impairment (see 4.2 Posology for dosage recommendations).

Administration during labour may cause respiratory depression in the new born infant (see 4.6 Pregnancy and lactation).

4.5 Interaction with other medicinal products and other forms of interaction

Alcohol: Alcohol can enhance the sedative and hypotensive effects of pethidine.

Anti-arrhythmics: Pethidine may delay absorption of mexiletine.

Antibacterials: The opioid analgesic papaveretum has been shown to reduce plasma ciprofloxacin concentration. The manufacturer of ciprofloxacin advises that premedication with opioid analgesics be avoided when ciprofloxacin is used for surgical prophylaxis.

Antidepressants, anxiolytics, hypnotics: Use with MAOIs, see 4.3 Contraindications. The depressant effects of pethidine may be exaggerated and prolonged by central nervous system depressants including tricyclic antidepressants, anxiolytics and hypnotics.

Antipsychotics: Enhanced sedative and hypotensive effect. Risk of toxicity with chlorpromazine, due to increased norpethidine levels.

Antidiarrhoeal and antiperistaltic agents (such as loperamide and kaolin): Concurrent use may increase the risk of severe constipation.

Antiepileptics: The depressant effect of pethidine may be exaggerated and prolonged by central nervous system depressants including phenobarbitone and phenytoin; also risk of toxicity due to increase norpethidine levels.

Antimuscarinics: Antimuscarinic agents such as atropine and other medications with antimuscarinic potential may have additive gastrointestinal and urinary tract effects. Consequently, severe constipation and urinary retention may occur during intensive therapy with combined antimuscarinics and opioid analgesics.

Antivirals: Ritonavir, see 4.3 Contraindications.

Dopaminergics: Selegiline, see 4.3 Contraindications.

Motility Stimulants: Pethidine has an antagonistic effect on metoclopramide and domperidone.

Ulcer healing drugs: Cimetidine may inhibit the metabolism of pethidine.

4.6 Fertility, pregnancy and lactation

As with all drugs used during pregnancy care should be taken in assessing the risk to benefit ratio.

There is inadequate evidence of safety in human pregnancy although pethidine has been used for many years without apparent ill consequence.

Pethidine is widely used for pain relief during labour and is known to cross the placenta and may cause respiratory depression in the new born infant. Withdrawal symptoms may occur in neonates of dependant mothers. During labour, gastric stasis, associated with the use of opioid analgesics, may increase the mother's risk of inhalation pneumonia.

Pethidine is excreted in breast milk and this should be taken into account when considering its use in patients during pregnancy or breast-feeding.

4.7 Effects on ability to drive and use machines

Pethidine causes drowsiness. Patients should not drive or use machines.

4.8 Undesirable effects

The most serious hazard of therapy is respiratory depression (see also 4.9 Overdose). The most common side-effects are sedation, nausea, constipation, dizziness, vomiting and sweating. Tolerance generally develops with long-term use, but not to constipation.

Other side-effects include the following:

Anaphylaxis: Anaphylactic reactions following intravenous injection have been reported rarely.

Cardiovascular: orthostatic hypotension, facial flushing, bradycardia, palpitations, tachycardia (frequent after intravenous administration).

Central Nervous System: vertigo, mental clouding, confusion (with large doses), mood changes including dysphoria and euphoria, restlessness, hallucinations, headache.

Disorders of the eye: miosis, blurred or double vision or other changes in vision.

Gastrointestinal: dry mouth, biliary spasm.

Skin: urticaria, pruritus, rash. Local reactions following injection.

Urinary: urinary retention, difficulty with micturition, ureteric spasm, antidiuretic effect. Tolerance develops to the effects of opioids on the bladder.

The euphoric activity of pethidine has led to its abuse and physical and psychological dependence may occur (see also section 4.4 Special Warnings and Precautions for use).

4.9 Overdose

Toxic doses vary considerably with the individual and regular users may tolerate large doses.

a) Symptoms

The triad of respiratory depression, coma or stupor and constricted pupils is considered indicative of opioid overdosage with dilatation of the pupils occurring as hypoxia develops.

Respiratory arrest and death may occur in severe overdose following rapid intravenous administration.

CNS excitatory effects include tremors, muscle twitches and convulsions attributed to the accumulation of the metabolite norpethidine.

Other opioid overdose symptoms include cold, clammy skin and hypothermia, muscle flaccidity, hypotension, bradycardia, circulatory collapse, cardiac arrest, confusion, severe dizziness, severe drowsiness, severe nervousness or restlessness, hallucinations, pulmonary oedema, rhabdomyolysis, progressing to renal failure.

b) Treatment

Respiration and circulation should be maintained and the patient should be observed closely. The specific opioid antagonist, naloxone is indicated if coma or bradypnoea are present, using one of the recommended dosage regimens. As the plasma half-life of naloxone is shorter than that of all opioid analgesics, repeated doses of naloxone may be required. All patients should be observed carefully for recurrence of CNS and respiratory depression for at least 6 hours after the last dose of naloxone.

A short acting muscle relaxant, intubation and controlled respiration may be needed to treat convulsions.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pethidine hydrochloride is a synthetic opioid analgesic which acts primarily on the central nervous system. It has a shorter duration of action than morphine. The analgesic effect lasts approximately two to four hours.

5.2 Pharmacokinetic properties

Pethidine is rapidly absorbed after subcutaneous or intramuscular injection with a peak plasma concentration usually occurring after 45 minutes. Pethidine is metabolised in the liver by hydrolysis to pethidinic acid or demethylation to norpethidine and hydrolysis to norpethidinic acid followed by partial conjugation with glucuronic acid.

The majority of the drug is excreted via the kidney as unchanged pethidine and its metabolite norpethidine.

Pethidine is 30%-50% bound to plasma proteins. The plasma half- life in man is three to six hours. The metabolite norpethidine which is pharmacologically active, is eliminated more slowly with a half life of up to 20 hours.

5.3 Preclinical safety data

There are no additional pre-clinical data of relevance to the prescriber.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for Injections

Hydrochloric acid)	for pH
Sodium hydroxide)	adjust ment

6.2 Incompatibilities

Pethidine Hydrochloride injection has been reported to be physically or chemically incompatible with solutions containing aminophylline, barbiturates (especially with thiopentone solution, which results in the formation of a pharmacologically inactive complex), heparin sodium, hydrocortisone sodium succinate, methyl prednisolone succinate, morphine sulphate, phenytoin sodium, sodium bicarbonate, sodium iodide, sulphadiazine sodium.

Pethidine hydrochloride has also been reported to be incompatible with aciclovir sodium, imipenern, frusemide, liposomal doxorubicin hydrochloride, idarubicin and solutions containing potassium iodide. Specialised references should be consulted for specific compatability information.

6.3 Shelf life

Three years

6.4 Special precautions for storage

Do not store above 25°C.

Keep ampoules in the outer carton.

6.5 Nature and contents of container

Neutral glass ampoules containing 1ml or 2ml of solution in cartons of 5, 10 or 50 ampoules.

6.6 Special precautions for disposal

The injection is for single patient use.

The injection should be given immediately after opening the ampoule. Once opened any unused portion should be discarded. The injection should not be used if particles are present.

For slow intravenous administration the contents of the ampoule may be diluted to 10ml with water for injections. Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C. From a microbiological point of view the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions.

7 MARKETING AUTHORISATION HOLDER

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LL13 9UF
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PL 29831/0174

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