SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PETHISOM 100mg/2ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

A 1 ml ampoule contains 50 mg pethidine hydrochloride. A 2 ml ampoule contains 100 mg pethidine hydrochloride.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Aqueous, clear, colourless solution, free of visible particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PETHISOM is indicated in adults and adolescents over 15 years of age for the short-term symptomatic treatment of acute, moderate to severe pain, justifying the use of a morphine analgesic.

4.2 **Posology and method of administration** This medicinal product is for hospital use only.

Posology

The posology should be adjusted according to the severity of the pain and the patient's response.

Adults and adolescents > 15 years old

A dose of pethidine hydrochloride 100 mg produces an analgesic effect comparable to a dose of approximately 10 mg of morphine administered intravenously and approximately 15 mg of morphine administered subcutaneously.

Intramuscular or subcutaneous route: 0.5 - 3.0 ml (25 -150 mg pethidine hydrochloride) per dose.

Intravenous route: 0.5 – 2.0 ml (25 – 100 mg pethidine hydrochloride) per dose, preferably as an infusion and diluted in 125 ml of 5% or 10% glucose solution or 0.9% sodium chloride, to be given over a period of 15 minutes in order to minimise the risk of serious respiratory problems or cardiovascular reactions.

In emergency, PETHISOM can also be administered as a slow intravenous injection (1 to 2 minutes), preferably diluted in 10 ml of a 5% or 10% glucose solution or 0.9% sodium chloride.

Repeated doses should be adjusted to the individual and are normally given at intervals of 3 to 4 hours, with a maximum dose of 500 mg per day, although higher doses are reported in the literature.

The administration of lower doses may be necessary when the patient has received medication that may induce respiratory depression or when the patient's respiratory function is impaired. This also applies to elderly patients or patients with hepatic or renal insufficiency (see below).

The dosage should also be adjusted according to the degree of analgesia obtained, the occurrence of adverse effects and the use of any other medication.

Treatment duration will be as short as possible.

Maximum recommended doses in adults and adolescents > 15 years:
Single dose: 100 mg
Dose per 24 hours: 500 mg

Elderly
In elderly patients it is recommended to reduce the initial dose and the total daily dose.

In case of renal insufficiency
No dosage adjustment is necessary in patients with mild renal insufficiency (Glomerular Filtration Rate greater than 50 ml/min). However, patients with moderate renal impairment (GFR 10 to 50 ml/min) should receive 75% of the normal dose at usual intervals.
Reduction of the initial dose of pethidine is recommended in patients with severe renal insufficiency (GFR less than 10 ml/min). These patients should receive 50% of the normal dose at the usual intervals.

In case of hepatic insufficiency
The initial dose of pethidine must be reduced in patients with severe hepatic insufficiency, potentially including hepatic insufficiency related to acute viral hepatitis or alcoholic cirrhosis.

Other cases
In debilitated patients or those with low body weight, administer a dose of 0.5 to 1.0 ml diluted with a solution of 5% or 10% glucose or 0.9% sodium chloride.
Administer the remainder of the ampoule (1.0 - 1.5 ml) intramuscularly. This dose produces an analgesic effect lasting for 2 to 4 hours.
The initial dose of pethidine must be reduced in patients with phaeochromocytoma, sickle cell anaemia, hypothyroidism, Addison's disease or prostatic hyperplasia and in patients with urethral stricture.

Paediatric population
The safety and efficacy of PETHISOM in children under 15 years of age have not been established.

Method of administration
Solution for injection for subcutaneous, intramuscular or intravenous route.
For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to pethidine, to morphine derivatives or to any of the excipients.
Dependence on opioids, medicinal products (especially psychotropic substances) or alcohol. PETHISOM cannot be used as substitution therapy in case of tolerance to opioids.
Convulsive disorders.
Severe hepatic insufficiency.

Respiratory failure due to bronchial asthma or COPD (Chronic Obstructive Pulmonary Disease).
Concomitant treatment (or less than 2 weeks earlier) with MAOIs (MonoAmine Oxidase Inhibitors).

Head trauma and situations associated with raised intracranial pressure, or in cases of consciousness disorders.
Abdominal syndrome before the establishment of the diagnosis.
Hypotension with hypovolaemia.
Children under 15 years old.
Third trimester of pregnancy.
Breast-feeding.

4.4 Special warnings and precautions for use

Pethidine should not be used for the treatment of chronic pain.
Pethidine may only be used for the treatment of episodes of acute, moderate to severe pain, in order to avoid adverse effects caused by the accumulation of the metabolite, norpethidine (see section 4.1).

Caution is required:

- In patients with hypothyroidism, adrenocortical insufficiency, respiratory insufficiency and shock (pethidine may accentuate the symptoms and the course of these conditions).
- In case of prostatic hypertrophy (pethidine may exacerbate urinary retention linked to utero- prostatic disorders).
- In case of supraventricular tachycardia (possible vagolytic effect).
- In case of hepatic or renal insufficiency and in elderly patients due to possible accumulation of pethidine or its active metabolites (see section 4.2).
- In the event of concomitant administration of other medicinal products with a depressant effect on the CNS (serious and even fatal interactions are possible – see section 4.5).
- In patients with a history of chronic alcoholism and dependence on other drugs (greater predisposition to dependence).

Pethidine is a narcotic that can lead to addiction: physical and psychological dependence as well as tolerance (decline in efficacy) following repeated administration or administration of high doses.
Symptoms of physical dependence can be agitation, nasal congestion, tearing, sleep disturbances, severe abdominal and muscle pain, nausea, vomiting, rapid breathing and accelerated heart rate. Gradual tapering of the doses of medicinal product helps to minimise withdrawal reactions.
To avoid withdrawal as well as toxicity from the active metabolite of pethidine (norpethidine), it is advised to use the lowest possible effective analgesic dose for the shortest possible period and to avoid using the medicinal product in the treatment chronic pain.
When using the parenteral form, a morphine antagonist and an antiepileptic should be

available.

Risk from concomitant use of sedatives such as benzodiazepines or related drugs: concomitant use of PETHISOM and sedatives, such as benzodiazepines or related drugs, may lead to sedation, respiratory depression, coma and death. Concomitant prescribing of these sedatives should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe PETHISOM concomitantly with sedatives, the lowest effective dose should be used and duration of treatment should be limited to the minimum necessary.
Patients should be strictly monitored for any signs or symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers of these symptoms (see section 4.5).

Some adverse effects are more pronounced after
- Intravenous injection, such as respiratory depression, CNS disorders, hypotension in the elderly and vagotropic effects (see section 4.8).
- Subcutaneous injection, such as tissue necrosis (see section 4.8).

Serotonin syndrome
Due to the risk of serotonin syndrome, pethidine should not be used in combination with serotonergic medicinal products (see section 4.5).

4.5Interaction with other medicinal products and other forms of interaction
Caution is advised when PETHISOM is administered at the same time as the following products:

Alcohol and other central depressant substances (anaesthetics, antipsychotics, anxiolytics, hypnotics): they can reinforce the depressant action on the central nervous system (increased risk of respiratory depression, reinforced sedation).

Phenothiazines: the use of pethidine in combination with phenothiazines has resulted in severe hypotension and may prolong respiratory depression following the administration of pethidine.

Barbiturates: morphine analgesics and barbiturates can be expected to have cumulative depressant effects on the central nervous system. The prolonged sedation observed on pethidine in the presence of phenobarbital has also been attributed to pethidine N-demethylation induction, resulting in increased formation of norpethidine, a potentially neurotoxic metabolite.

Sedatives such as benzodiazepines or related drugs: concomitant use of opioids and sedatives, such as benzodiazepines or related drugs, increases the risk of sedation, respiratory depression, coma and death due to depressant effects CNS additives. The doses and duration of concomitant use should be limited (see section 4.4).

MAOIs: very severe reactions, including coma, severe respiratory depression, cyanosis and hypotension have been observed in patients taking MAOIs (including moclobemide and selegiline) who have received pethidine. Cases of greatly increased irritability, convulsions, tachycardia, hyperpyrexia and hypertension have also been reported. Pethidine should not be administered to patients on MAOIs or in whom the administration of MAOIs was discontinued less than 14 days earlier (see section 4.3.)

Ritonavir: plasma levels of norpethidine are increased by ritonavir administration, with a consequent risk of toxicity; their simultaneous use should be avoided.
Phenytoin: the hepatic metabolism of pethidine seems to be reinforced by phenytoin; their combined use resulted in a decrease in the half-life and bioavailability in healthy subjects; norpethidine blood levels were increased.

Morphine-like medicinal products with agonist-antagonist action (derivatives of pentazocine and buprenorphine): they can weaken the action of pethidine because of competitive binding to opioid receptors and in case of physical dependence, they can create withdrawal symptoms.

Cimetidine: increases pethidine toxicity by decreasing its metabolism, which may manifest as respiratory depression, CNS depression and hypotension.

Serotonergic medicinal products: cases of serotonin syndrome have been reported in patients using pethidine concomitantly with serotonergic drugs such as the selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRIs), and with St. John's wort (*Hypericum perforatum*) (see section 4.4).

4.6 Pregnancy and lactation

Pregnancy

There are limited data on the use of pethidine in pregnant women. Animal studies are insufficient to conclude on reproductive toxicity (see section 5.3).

The administration of pethidine in late pregnancy, when administered during labour, significantly decreases foetal heart rate and may cause respiratory depression and sucking reflex disorders in the neonate (see section 4.8). In addition, pethidine is metabolised to norpethidine, an active metabolite which accumulates in the foetus due to a long half-life. The neonatal impact relates to neurobehavioural functions and depends on the total dose received and the injection-birth interval. Therefore:

- The use of pethidine is **not recommended during the first and second trimesters of pregnancy**.
- The use of pethidine is **contraindicated during the third trimester of pregnancy** (see section 4.3).

Breastfeeding

Pethidine is excreted in breast milk. A few cases of low muscle tone and respiratory pauses have been described in infants after ingestion of morphine derivatives at supra-therapeutic doses by the mothers.
Breastfeeding is therefore contraindicated (see section 4.3)

Fertility

No data is available.

4.7 Effects on ability to drive and use machines

Even when PETHISOM is used as prescribed, decreased alertness and vertigo may occur to such an extent that the patient is no longer able to drive or operate machinery. The consumption of alcohol can further enhance this effect.

4.8 Undesirable effects

The sedative and tranquilising effects of pethidine are comparable to those of morphine, but the analgesia and respiratory depression produced are of shorter duration and it induces less muscle spasm.
With the exception of cutaneous adverse effects, all adverse effects involve opioid receptors.

The undesirable effects of pethidine described in literature are presented hereunder and are classified by System Organ Class and by frequency. Frequencies are defined as following: 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).

Organ system	Undesirable effects	Frequency
Immune system disorders	Erythema, facial oedema, pruritus, increased heart rate, pallor, sweating, feeling cold in the arms and legs, feeling unwell, altered state of consciousness.	Not known
	Anaphylactic shock	Rare
Nervous system disorders	Confusion*, sedation, irritation, headache, dizziness*, euphoria, dysphoria with anxiety and agitation, hallucinations.	Common
	Asthenia, delirium, disorientation.	Not known
Eye disorders	Miosis*.	
Cardiac disorders	Bradycardia*, hypotension*.	Common
	Hypertension, tachycardia*, syncope, palpitation, cardiac arrest, bradyarrhythmia.	Not known
Respiratory, thoracic and mediastinal disorders	Respiratory depression.	Common
	Bronchospasm*.	Not known
Gastrointestinal disorders	Hiccups*, constipation*, nausea*, vomiting*.	Common
	Abnormal taste in mouth.	Not known
Hepatobiliary disorders	Biliary tract spasms, transient increase in transaminases.	Not known
Skin and subcutaneous tissue disorders	Pruritus, urticaria, other rashes, dry mouth, sweating, redness.	Not known
Musculoskeletal and connective tissue disorders	Tremor, muscle pain, muscle rigidity (after high doses).	Not known
Renal and urinary disorders	Urinary retention.	Not known
General disorders and administration site conditions	Pain at the injection site (if IV), formation of red, itchy bumps along the vein.	Rare

*Major vagotropic effects are possible especially after intravenous injection; they can be counteracted with a low dose of atropine.

Anaphylactic shock is rare but may occur during the injection. It is potentially fatal.

The use of PETHISOM can induce **physical and psychological dependence**, which

increases with the duration of use and the dose. We will therefore be attentive to the possible occurrence of withdrawal phenomena: mydriasis, tearing, rhinorrhoea, tremor, headache, profuse sweating, anxiety, insomnia.

The excitatory effects of pethidine on the central nervous system such as tremor, muscle twitching and convulsions have been linked to toxic doses and were attributed to the metabolite, norpethidine. Accumulation of norpethidine may occur after repeated administration at short intervals of high doses of pethidine (including in the context of PCA – *patient-controlled analgesia*). Probably more particularly in the presence of impaired renal function.

In obstetrics, adverse effects are also possible in newborn infants. Close attention should be paid to respiratory depression. The infant should therefore be monitored until there is no longer any risk of respiratory depression, but a morphine antagonist (e.g. naloxone) should be given for at least 24 hours depending on the clinical condition.

Special population
In patients with phaeochromocytoma, pethidine may trigger a hypertensive crisis.
Due to slower elimination, the risk of toxicity may be greater in the elderly and in people with hepatic or renal insufficiency (see sections 4.4 and 4.2).

4.9 Overdose

Symptoms
Visual disturbances, dry mouth, tachycardia, dizziness, drunkenness with mydriasis, increased body temperature, muscle fibrillation, hypotension followed by respiratory depression, anaesthesia, sudden loss of consciousness.

Severe IV overdose may cause apnoea, circulatory collapse and death.

Treatment
Respiratory depression: specific morphine antagonists (e.g. naloxone, to be repeated if necessary). Free or keep the airways free (lateral decubitus, aspiration, intubation, etc.).
If necessary, perform artificial respiration.
The following substances **cannot** be used: alcohol, barbiturates, phenothiazine derivatives, scopolamine.

Measures in case of anaphylactic shock:
At the first signs (sweating, nausea, cyanosis), interrupt the injection, leave the needle in place, or seek venous access. In addition to the usual emergency measures, lay the patient down with the legs elevated and keep the airways clear and free.

Emergency drug treatment:
Administer adrenaline (epinephrine) by slow IV injection.
Check pulse and blood pressure, paying attention to any arrhythmias. If necessary, repeat the injection of adrenaline. Then inject IV glucocorticoids, e.g. methylprednisolone. Repeat if necessary.
Then restore blood volume with plasma substitutes, human albumin or an electrolyte solution.

Other therapeutic measures:
Artificial respiration, oxygen therapy, antihistamines.

5 PHARMACOLOGICAL PROPERTIES

5.1 **Pharmacodynamic properties** Pharmacotherapeutic group: opioid analgesic. ATC code: N02AB02
PETHISOM IS SUBJECT TO NARCOTIC CONTROL REGULATIONS.

Pethidine is a morphine-like centrally-acting analgesic. Pethidine blocks the neurotransmission of nociceptive messages and modifies the patient's mental reaction to pain. The analgesic action of pethidine is five to ten times weaker than that of morphine (60 to 80 mg are equivalent to 10 mg of morphine). It has a depressant effect on respiration, antagonised by the administration of naloxone. Norpethidine, the main active metabolite of pethidine, has one half the analgesic power of the latter and causes convulsions.

5.2 Pharmacokinetic properties

Absorption
Pethidine is well absorbed by all recommended routes of administration.

Distribution
Depending on the dose, analgesia is maintained for 2 to 4 hours. Peak plasma concentrations are reached 15 minutes after an intramuscular injection. After subcutaneous administration of 50 to 75 mg of pethidine, plasma levels of 200 to 400 ng/ml are observed after one hour.
60% of the pethidine dose is plasma protein bound. Its plasma half-life is 3 to 4 hours.

Its distribution is rapid in the most vascularised tissues ($t_{1/2} \simeq 7.6$ min). The volume of distribution is between 2.8 and 4.7 l/kg.

Biotransformation
Pethidine is metabolised in the liver by hydrolysis to pethidinic acid or by demethylation to norpethidine and hydrolysis to norpethidinic acid, followed by glucuronic acid conjugation. About 1/3 of the pethidine administered can be found in the urine in the form of N-demethylated derivatives. Accumulation of norpethidine can lead to toxicity.
The $t_{1/2}$ of norpethidine is estimated at 20 hours.

Elimination
Pethidine, norpethidine and their metabolites are eliminated via the kidneys. For pethidine the elimination half-life is 3.6 hours and for norpethidine, 8 hours.
Excretion of pethidine and norpethidine is increased by acidification of the urine and reduced by alkalinisation of the urine.
The elimination of these compounds is slower in patients with cirrhosis and in those with renal failure. Excretion of norpethidine is delayed in patients with renal failure.

Special populations
The half-life of pethidine can reach 7 to 11 hours in case of cirrhosis or active viral hepatitis due to impaired metabolism of the medicinal product in the liver. This could increase the risk of cumulative toxicity due to slower elimination of the metabolite (see section 4.2).

Plasma protein binding of pethidine is lower in patients with renal disease. It can be approximately 31.8% in case of anuria. Also, a slower elimination of the norpethidine metabolite has been reported. This may cause it to accumulate and cause serious side effects (e.g. convulsive seizures) (see section 4.2).

Pethidine crosses the placental barrier and is also excreted in breast milk.
In newborn infants, the measured plasma half-life is 6.5 to 39 hours, i.e. 2 to 7 times higher than in adults (see section 4.6).

5.3 Preclinical safety data
There are no non-clinical data relevant for the prescriber other than those already mentioned in the scientific leaflet.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Water for injections.

6.2 Incompatibilities
Do not mix PETHISOM with aminophylline, amylobarbital sodium salts, heparin, methicillin, pentobarbital, phenobarbital, phenytoin, sulfadiazine, thiopental, bicarbonate, sodium iodide, morphine sulphate, sulphafurazole and diethanolamine.

This medicinal product must not be mixed with other medicinal products or solvents except those mentioned in section 6.6.

6.3 Shelf life

Before ampoule opening 5 years.

After ampoule opening
This medicinal product does not contain any antimicrobial preservative and should be used immediately after the ampoule opening.

After dilution
Chemical and physical in-use stability of the diluted product in glucose 5% and 10% or sodium chloride 0.9% has been demonstrated for up to 24 hours at room temperature (15 - 25°C).

From a microbiological point of view, unless the method of opening/dilution precludes the risks of microbial contamination, the diluted product should be used immediately after preparation. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions. For storage

conditions of the diluted medicinal product, see section 6.3.

6.5 **Nature and contents of container** PETHISOM 50mg/1ml: 1 ml glass ampoules.

PETHISOM 100mg/2ml: 2 ml glass ampoules. Pack sizes containing 5, 10 or 100 ampoules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For infusion, PETHISOM can be diluted in 125 ml of a 5% or 10% glucose solution or 0.9% sodium chloride solution (see section 4.2).
For slow IV injection, PETHISOM can be diluted in 10 ml of a 5% or 10% glucose solution or 0.9% sodium chloride solution (see section 4.2).
Do not use the solution if it is not clear or if it contains particles or a precipitate.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESSES

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