SUMMARY OF PRODUCT CHARACTERISTICS

hameln

Pethidine-hameln 50 mg/ml Injection

1. NAME OF THE MEDICINAL PRODUCT

Pethidine-hameln 50 mg/ml Injection
Active substance: pethidine hydrochloride

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ampoule of 1 ml solution for injection contains 50 mg pethidine hydrochloride.
1 ampoule of 2 ml solution for injection contains 100 mg pethidine hydrochloride.
Excipients with known effect:
1 ml solution for injection contains up to 0.0172 mg sodium.
For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Severe pain.

4.2 Posology, method and duration of administration

Dosage

Adults
The individual dose is:
- for intramuscular and subcutaneous administration: 25-150 mg pethidine hydrochloride and
- for intravenous administration: 50 mg pethidine hydrochloride (equivalent to 0.7 mg pethidine hydrochloride per kg body weight).

Essentially, the smallest effective analgesic dose should be selected. If, as an exception, Pethidine-hameln is to be used to treat chronic pain, the dose should preferably be administered according to a set schedule.
The individual dose can be repeated at 3-6 hour intervals.
Any further increase in individual doses does not produce an enhanced analgesic effect but merely exacerbates the side effects.
A single dose is often sufficient to treat acute pain. If necessary, Pethidine-hameln can be administered repeatedly and with special care over several days.
The daily dose should not exceed 500 mg pethidine hydrochloride.
Pethidine should not be used for prolonged periods due to the high neurotoxicity of the main metabolite norpethidine.

Patients with liver and kidney dysfunction
Liver failure can cause an increased concentration of pethidine in the blood so the dose must be reduced accordingly.
In cases of renal dysfunction, the interval between doses must be extended and/or the dose reduced to prevent an accumulation of active metabolites of pethidine.

Elderly patients
For elderly patients, the dose should be reduced (see section 4.4).

Children and adolescents
There is no empirical data available on safety of use for Pethidine-hameln among children and adolescents aged under 16 years. The solution for injection is not suitable for these patients due to the high content of active ingredient. For this purpose, other forms of administration (e.g. oral drops, solution) are available.

Method of administration
The solution is mainly administered by intramuscular injection into the largest possible muscle. However, it can also be administered subcutaneously or intravenously.
The intravenous injection must be administered slowly (i.e. over 1-2 minutes) to minimise any possible side effects.

4.3 Contraindications

Pethidine-hameln must not be used in patients with:
- hypersensitivity to the active substance or to any of the excipients listed in section 6.1,
- concomitant treatment with monoamine oxidase inhibitors or within 14 days of their withdrawal (see also section 4.5),
- severe respiratory depression,
- children and adolescents aged under 16 years due to the high content of active ingredient in the injection solution (see also section 4.2).

4.4 Special warnings and precautions for use

Do not use Pethidine-hameln to treat chronic pain. Pethidine-hameln should only be used to treat acute episodes of severe pain in order to avoid secondary side effects due to the accumulation of the metabolite norpethidine.
Take special care with Pethidine-hameln in
- patients with dependence on opioids or other substances (e.g. alcohol, medicinal products),
- patients with impaired consciousness,
- patients with disorders of the respiratory centre and respiratory function or pathologies where suppression of the respiratory centre is to be avoided,
- patients with head injuries or raised cerebral pressure,
- patients with hypotension, hypovolaemia,
- patients with liver dysfunction (e.g. cirrhosis of liver) and patients with renal dysfunction (due to accumulation of pethidine and/or its active metabolites),
- patients with a history of epileptic seizures,
- patients with hypo- or hyperthyroidism,
- patients with adrenal insufficiency (e.g. Addison's disease),
- patients with supraventricular tachycardia,
- patients with disorders of the prostate (e.g. prostatic hypertrophy) and urethra (e.g. urethral stenosis) (risk of urine retention),
- patients with acute abdominal symptoms,
- elderly patients (dose reduction recommended).

Dependency potential and withdrawal syndrome
Pethidine-hameln has a primary dependency potential.
Tachyphylaxis and physical and mental dependency develop with prolonged use. There is cross-tolerance to other opioids. When long-term treatment is suddenly terminated, symptoms of a withdrawal syndrome can occur (see also section 4.2). These symptoms include mental symptoms such as agitation, anxiety, irritation, depression and/or vegetative symptoms such as sweating, abdominal cramps, vomiting, circulatory failure etc.
With medicinal products that act on the CNS, there is essentially the risk of abuse. Before prescribing Pethidine-hameln to patients who are or have been dependent on alcohol or pharmaceuticals or who have a tendency to abuse of prescription medications, the indication should be carefully checked and administration of Pethidine-hameln closely monitored.
Risks from concomitant use with Benzodiazepines
Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Pethidine-hameln with benzodiazepines. Observational studies have demonstrated that concomitant use of opioids and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.
If the decision is made to newly prescribe a benzodiazepine and an opioid together, prescribe the lowest effective dosages and minimum durations of concomitant use.
If the decision is made to prescribe a benzodiazepine in a patient already receiving an opioid, prescribe a lower initial dose of the benzodiazepine than indicated in the absence of an opioid, and titrate based on clinical response.
If the decision is made to prescribe an opioid in a patient already taking benzodiazepine, prescribe a lower initial dose of the opioid, and titrate based on clinical response.
Follow patients closely for signs and symptoms of respiratory depression and sedation. Advise both patients and caregivers about the risks of respiratory depression and sedation when Pethidine-hameln is used with benzodiazepines. Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of benzodiazepines (see section 4.5.)
Serotonin Syndrome with Concomitant Use of Serotonergic Drugs
Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concurrent use of Pethidine-hameln with serotonergic drugs (see section 4.5). This may occur within the recommended dosage range.
Serotonin syndrome symptoms may include mental-status changes (e.g. agitation, hallucinations, coma), autonomic instability (e.g. tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g. hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhea) and can be fatal (see section 4.5). The onset of symptoms generally occurs within several hours to a few days of concomitant use, but may occur later than that. Discontinue Pethidine-hameln if serotonin syndrome is suspected.
Adrenal insufficiency
Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, decreased appetite, fatigue, weakness, dizziness and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement dosing of corticosteroids. Wean the patient of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.
Sexual function/Reproduction
Long term use of opioids may be associated with decreased sex hormone levels and symptoms such as low libido, erectile dysfunction, or infertility (see section 4.8).
Risks from concomitant use with other CNS depressants/alcohol
Concomitant use of opioids, including Pethidine-hameln, with alcohol may result in sedation, respiratory depression, coma, and death. Avoid drinking alcohol during treatment with pethidine.
With concomitant use of other centrally suppressant medicinal products such as morphine or barbiturates there is an increased risk of respiratory depression, which may prove fatal.
Seizures
Take special care if there is a history of seizures.
In cases of renal dysfunction, intervals between doses should be extended and/or the dose reduced as otherwise seizures may occur due to accumulation of the metabolite norpethidine. In cases of epilepsy, Pethidine-hameln should only be administered together with an anticonvulsant.
Instructions for injection
Following i.v. injection respiratory depression may be more common and more severe.
Excitatory effects on the central nervous system (tremor, involuntary muscle spasms etc.) occur more frequently following parenteral injection and at a higher dose.
In elderly patients, even at the recommended dose, critical hypotension can occur with i.v. injection.
After repeated i.m. injection, fibrous myopathies were observed.
Using Pethidine-hameln may produce positive results in dope tests. Using Pethidine-hameln as a doping agent may also damage health.
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. it is almost "sodium-free".

4.5 Interactions with other medicinal products and other interactions

Ritonavir
Plasma levels of the metabolite norpethidine may be increased by ritonavir, so take care with concomitant use.
Phenytoin
The hepatic metabolism of pethidine may be enhanced by phenytoin. Concomitant administration may lead to a reduced half-life and bioavailability of pethidine and a raised level of norpethidine, so take care with concomitant use.
Cimetidine
Cimetidine reduces the clearance and distribution volume of pethidine as well as formation of the metabolite norpethidine, so take care with concomitant use.
Benzodiazepines
Due to additive pharmacologic effect, the concomitant use of opioids with benzodiazepines increases the risk of respiratory depression, profound sedation, coma and death.
The concomitant use of opioids and benzodiazepines increases the risk of respiratory depression because of actions at different receptor sites in the central nervous system that control respiration. Opioids interact primarily at μ-receptors, and benzodiazepines interact at GABAA sites. When opioids and benzodiazepines are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists.
Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate (see section 4.4).
Limit dosage and duration of concomitant use of benzodiazepines and opioids, and follow patients closely for respiratory depression and sedation.
Other CNS depressants
Use with barbiturates and other CNS depressant drugs may result in a decreased state of consciousness or respiratory depression due to the additive CNS depressant effect. Therefore, caution is advised when used concomitantly.
Alcohol
Concomitant use of alcohol with opioids increases the risk of sedation, respiratory depression, coma, and death due to the mutual enhancement of the central depressant effect.
Phenothiazines
Concomitant use of pethidine and phenothiazines can increase the risk of hypotension.
Phenobarbital
Using Pethidine-hameln and long-term therapy with phenobarbital results in increased metabolism of pethidine. An increased risk of side effects cannot be ruled out.
Pentazocine, nalbuphine and buprenorphine
Using pethidine together with partial opioid-receptor antagonists (pentazocine, nalbuphine and buprenorphine) can result in a reduced analgesic effect and lead to symptoms of withdrawal due to the competitive receptor antagonism.
MAO inhibitors
There have been reports of interactions leading to potentially fatal effects on the central nervous system, respiration and circulation with pethidine in cases where patients have previously been treated with MAO inhibitors within 14 days prior to administering the opioid. There have been reports of a serotonin

syndrome with agitation, hyperthermia, diarrhoea, tachycardia, sweating, tremor and (pre-)syncope and a condition similar to opioid overdose with coma, severe respiratory depression and hypotension.

Serotonergic drugs

The concomitant use of opioids with other drugs that affected the serotonergic neurotransmitter system has resulted in serotonin syndrome. If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue Pethidine-hameln if serotonin syndrome is suspected. Examples of serotonergic drugs are selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g.mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue) (see section 4.4).

Take care when combined with other strong-acting analgesics and anticonvulsants.

4.6 Fertility, pregnancy and lactation

Pregnancy

Using Pethidine-hameln during pregnancy and during labour is not recommended as there is insufficient empirical data available. To date there have been no reported signs of any increased risk of congenital defects in humans.

Chronic use of pethidine is to be avoided throughout pregnancy as it may lead to foetal dependency and postpartum withdrawal symptoms.

During labour, pethidine should be administered only by intramuscular injection at the lowest possible dose. Pethidine does not impair the normal contraction of the uterus.

After administering pethidine during labour:

- it may cause respiratory depression, lower heart rate, and attenuated behavioural neurological functions, including feeding difficulties in the neonate as pethidine crosses the placenta (this effect depends on the dose and time),
- there have been reports of impaired behaviour and EEG changes in the neonate for up to six days postpartum and
- the ability to survive of at-risk infants may be further impaired.

The neonate must therefore be monitored until no further major impairment of breathing is to be expected (and for at least 6 hours). Depending on the clinical profile (especially mindful of the breathing problems postpartum) it is recommended administering opiate antagonists (e.g. naloxone) to the neonate.

Empirical data in humans to date with approx. 270 pregnancies with exposure during the first trimester have produced no evidence of any teratogenic risk. A possible link with the onset of inguinal hernias cannot be ruled out.

Lactation

Pethidine and its metabolite norpethidine pass into breast milk. Patients should be advised to discontinue breastfeeding during repeated treatment with Pethidine-hameln, as severe side effects may occur in the nursing infant, that may be delayed and last for days to weeks. Therefore, the benefit of breastfeeding to the infant must be weighed against the benefit of the treatment for the mother and a decision taken over whether to terminate breastfeeding or treatment with pethidine.

4.7 Effects on ability to drive and use machines

The patient must be informed that they are no longer able to drive and use machines whilst taking Pethidine-hameln due to impaired concentration and confusion.

4.8 Adverse effects

Very common:	≥1/10;
Common:	≥1/100, <1/10;
Occasionally:	≥1/1000, <1/100;
Rarely:	≥1/10 000, <1/1000;
Very rarely:	<1/10 000;
Unknown:	Incidence cannot be assessed based on available data.

Disorders of the immune system

Incidence unknown

Hypersensitivity reactions (anaphylaxis, possibly ranging through to potentially fatal shock).

Hypotension and/or tachycardia, flushing, sweating and pruritus due to release of histamine.

Psychiatric disorders

Common

Confusion, mood changes (mostly euphoria, occasionally dysphoria), changes in cognitive and sensory capacity (e.g. ability to make decisions as well as perception problems). This may also include states of excitation, mania, hallucinations etc. [1])

Incidence unknown

Disorientation, delirium, dependency on prescription drugs, withdrawal syndrome.

Disorders of the nervous system

Common

Sedation, dizziness.

Incidence unknown

Tremor, involuntary muscle movements, seizures (especially at higher doses, in patients with impaired renal function and in patients with [e.g. drug-induced] increased tendency to convulsions).

Eye disorders

Incidence unknown

Miosis (especially following rapid intravenous administration).

Cardiac disorders

Incidence unknown

Myocardial infarction (as part of a Kounis syndrome), tachycardia, bradycardia.

Vascular disorders

Incidence unknown

Hypotensive circulatory reactions.

Disorders of the airways, thorax and mediastinum

Common

Respiratory depression. [2])

Incidence unknown

Bronchospasm, hiccough (both especially following rapid intravenous administration).

Disorders of the gastrointestinal tract

Incidence unknown

Nausea, vomiting (both especially following rapid intravenous administration).

Constipation (due to an increased smooth muscle tone in the gastrointestinal area especially with prolonged use), dry mouth.

Disorders of the liver and gall bladder

Incidence unknown

Contraction of the gall ducts.

Disorders of the kidneys and urinary tract

Incidence unknown

Micturition problems such as urinary retention (due to an increased smooth muscle tone in the urinary tract area, especially with prolonged use).

General disorders and symptoms at the administration site

Incidence unknown

Tachyphylaxis. Pain at the injection site. With i.v. injection: Skin redness and hives (urticaria) along the affected vein.

With i.m. injection: Muscle necrosis, nerve damage.

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[1]) The various psychological side effects occur individually in terms of strength and type (depending on personality and duration of medication).

[2]) In equal analgesic doses pethidine causes roughly the same degree of respiratory depression as morphine. This can lead to an increase in the CO2 concentration with subsequent increase in intracranial pressure, so Pethidine-hameln should not be used in cases of increased intracranial pressure. See also section 4.4.

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.

Postmarketing Experience:

Serotonin syndrome (see section 'Warning and Precautions')

Adrenal insufficiency (see section 'Warning and Precautions')

Androgen deficiency:

Cases of androgen deficiency have occurred with chronic use of opioids. Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The casual role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.

Infertility:

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible.

4.9 Overdose

Typical symptoms of overdose are miosis and respiratory depression ranging through to respiratory arrest. It may also result in impaired consciousness ranging through to coma, low blood pressure, tachycardia, dizziness, muscle spasms, high temperature, delirium, hypothermia and with increasing hypoxaemia to mydriasis. Severe overdose, especially after i.v. administration, may result in respiratory arrest, circulatory arrest and death.

These effects can be alleviated by administering opiate antagonists (e.g. naloxone). This must be administered cautiously in repeated small doses as the duration of effect is shorter than that of pethidine.

Further measures are

- with oral use: primary toxin removal through gastric lavage and absorption reduction by administering medicated charcoal,
- circulation stabilisation by electrolyte infusion as well as improvement of respiratory function by oxygen inhalation and controlled ventilation.

The possibility of multiple intoxication should always be considered (alcohol, psychoactive substances; with attempted suicide).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: analgesics, opioids, phenylpiperidine derivative.

ATC code: N02AB02.

Pethidine is a phenylpiperidine derivative with opiate agonist properties. It displays a pronounced affinity to mu receptors and slight affinity to delta and kappa receptors. Pethidine has a strong analgesic, antitussive, sedative and respiratory depressive effect. It lowers blood pressure and raises heart rate.

5.2 Pharmacokinetic properties

Following intravenous administration of 25 mg pethidine hydrochloride maximum plasma levels of 100-200 ng/ml have been achieved within 15 minutes with comparable maximum plasma levels following intramuscular administration. The absorption half-life was 7-18 min and the bioavailability was 93-98 %.

Plasma-protein binding of pethidine is between 37-73 %.

Key metabolites of pethidine are pharmacologically active norpethidine and carboxylic acids resulting from hydrolysis of pethidine and norpethidine, which are excreted mostly in conjugated form. Other metabolites occurring in smaller quantities are pethidine-N-oxide, 4-hydroxypethidine, norpethidine-N-oxide and N-hydroxynorpethidine.

A plasma half-life of 3.2-8 hours has been measured for pethidine, compared to 8-12 hours for norpethidine.

Pethidine and its metabolites are largely excreted via the kidneys. 65.4 % of the dose has been measured in 24-hour urine.

In 24-hour urine, 5-10 % pethidine, 7-13 % norpethidine, 5-7 % free pethidinic acid, 13 % pethidinic acid glucuronide, 4-10.5 % norpethidinic acid and 16 % norpethidinic acid glucuronide were detected.

With renal dysfunction, norpethidine can accumulate and cause severe side effects (seizures).

Pethidine crosses the placenta almost unhindered and is also excreted into breast milk.

In neonates a plasma half-life of 6.5-39 hours has been measured for pethidine, which was 2-7 times more than with adults.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide solution

Water for injection

6.2 Incompatibilities

Pethidine-hameln should essentially not be administered mixed with other medicinal products.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30°C.

Do not freeze.

Keep the container in the outer carton in order to protect from light.

Keep out of reach of children.

Jauhi daripada kanak-kanak.

6.5 Nature and contents of container

1 ml:

Pack of 5 ampoules containing 1 ml each

Pack of 10 ampoules containing 1 ml each

2 ml:

Pack of 5 ampoules containing 2 ml each

Pack of 10 ampoules containing 2 ml each

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

None.

7. PRODUCT REGISTRANT / MANUFACTURER

Product Registrant Malaysia

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(125824-M)
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Product Registrant Singapore

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Singapore 118530

Manufacturer

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Langes Feld 13, 31789 Hameln
Germany

8. MARKETING AUTHORISATION NUMBER(S)

Malaysia	MAL19992692ACZ
Singapore	SIN14662P

9. DATE OF REVISION OF THE TEXT

03/2024