Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Palladone 20 mg/ml, solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Palladone ***20 mg/ml:***
1 ampoule contains 20 mg hydromorphone hydrochloride (corresponding to 17.73 mg hydromorphone) in 1 ml solution.
Excipient: 1 ml contains 0.105 mmol of sodium (2.41 mg/ml of sodium)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection or infusion.
Clear, colourless to pale yellow, pH 4.0 solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the treatment of severe pain.

4.2 Posology and method of administration

Method of administration

Intravenous injection or infusion
Subcutaneous injection or infusion

The medicinal product is to be visually inspected prior to use and also after dilution. Only clear solutions practically free from particles should be used.

The injection should be given immediately after opening the ampoule. Once opened, any unused portion should be discarded.

Posology

The dosing of Palladone has to be adjusted to the patients' severity of pain and to their individual response.

The dose should be titrated until optimum analgesic effect is achieved.

While a sufficiently high dose should generally be administered, the smallest dose to achieve analgesia should be aimed at in the individual case.

Palladone 10 mg, 20 mg and 50 mg are not suitable for initial opioid therapy. These higher dosage forms may only be used as individual doses in patients who have no longer sufficiently responded to lower doses of hydromorphone preparations.

Palladone should not be administered longer than absolutely necessary. If long-term treatment is required careful and regular monitoring should control whether and to what degree further treatment is necessary. When

a patient no longer requires therapy with hydromorphone, it may be advisable to taper the daily dose gradually to prevent withdrawal symptoms.

Age	Bolus	Infusion
Adults and adolescents (> 12 years)		
subcutaneous (s.c.) use	1-2 mg s.c. every 3-4 hours	0.15-0.45 mg/h 0.004 mg/kg bodyweight/h
intravenous (i.v.) use	1-1.5 mg i.v. every 3-4 hours to be injected slowly over at least 2-3 minutes	0.15-0.45 mg/h 0.004 mg/kg bodyweight/h
PCA (s.c. and i.v.)	0.2 mg bolus, stop interval 5-10 min.	
Children (< 12 years)	Not recommended	

Transferring patients between oral and parenteral hydromorphone:
The dose should be based on the following ratio: 3 mg of oral hydromorphone is equivalent to 1 mg of intravenously administered hydromorphone. It must be emphasised that this is a guide to the dose required. Inter-patient variability requires that each patient is carefully titrated to the appropriate dose.

Children (< 12 years)
Palladone is not recommended for use in children under 12 years of age due to insufficient data on safety and efficacy.

Elderly patients
Elderly patients (as a rule over 75 years) may require a lower dosage than other adults to achieve adequate analgesia.

Patients with hepatic and/or renal impairment
These patients may require lower doses than other patient groups to achieve adequate analgesia. They should be carefully titrated to clinical effect (see Section 5.2).

4.3 Contraindications

Hypersensitivity to hydromorphone or to any of the excipients. Significant respiratory depression with hypoxia or elevated carbon dioxide levels in the blood, severe chronic obstructive pulmonary disease, cor pulmonale, coma, acute abdomen, paralytic ileus, simultaneous administration of mono-amine oxidase inhibitors or within two weeks of discontinuation of their use.

4.4 Special warnings and precautions for use

The major risk of opioid excess is respiratory depression. Hydromorphone should be used with caution in opioid-dependent patients, in patients with head injury (due to the risk of increased intracranial pressure), convulsive disorders, alcoholism, delirium tremens, toxic psychosis, hypotension with hypovolaemia, disorders of consciousness, biliary tract diseases, biliary or ureteric colic, pancreatitis, obstructive or inflammatory bowel disorders, prostatic hypertrophy, adrenocortical insufficiency (e.g. Addison’s disease), hypothyroidism, chronic obstructive pulmonary disease, reduced respiratory reserve, in children under 12 years, in debilitated, elderly or infirm patients and in patients with severely impaired renal or hepatic function (see Section 4.2). In all these patients, reduced dosage may be advisable.

The patient may develop tolerance to Palladone with prolonged use and require progressively higher doses to achieve the desired analgesic effect. There may also be cross-tolerance with other opioids. Chronic use of Palladone may lead to physical dependence and a withdrawal syndrome may occur upon abrupt cessation of therapy. When a patient no longer requires therapy with hydromorphone, it may be advisable to taper the daily dose gradually to prevent withdrawal symptoms.

Hydromorphone has an abuse potential similar to other strong opioid agonists. Hydromorphone-containing medicinal products may be sought and abused by people with latent or manifest addiction disorders. There is potential for development of psychological dependence (addiction) to opioid analgesics, including Palladone. Therefore, Palladone should be used with particular care in patients with a history of alcohol and drug abuse.

Hyperalgesia that will not respond to a further dose increase of Palladone may very rarely occur in particular in high doses. A hydromorphone dose reduction or change in opioid may be required.

Palladone should not be used where the occurrence of paralytic ileus is possible. Should paralytic ileus be suspected or occur during use, hydromorphone treatment must be discontinued immediately.

Palladone should be used with caution pre- or intraoperatively and within the first 24 hours postoperatively.

Patients about to undergo additional pain-relieving procedures (e.g. surgery, plexus blockade) should not receive hydromorphone for 4 hours prior to the intervention. If further treatment with Palladone is indicated, the dosage should be adjusted to the post-operative requirement.

It should be emphasised that patients, once adjusted (titrated) to an effective dose of a specific opioid, should not be changed to other opioid analgesics without clinical assessment and careful retitration as necessary. Otherwise a continuous analgesic action is not ensured.

The use of hydromorphone may produce positive results in doping controls.

This medicinal product contains less than 1 mmol sodium (23 mg) per ml, i.e. essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

Centrally acting medicinal products such as tranquillisers, anaesthetics (e.g. barbiturates), hypnotics and sedatives, neuroleptics, antidepressants, antiemetics, antihistamines and other opioids or alcohol may enhance the CNS depressant effects of either drug, e.g. sedation, respiratory depression.

Medicinal products with an anticholinergic effect (e.g. psychotropics, antiemetics, antihistamines or antiparkinsonian medicinal products) may enhance the anticholinergic undesirable effects of opioids (e.g. constipation, dry mouth or urinary retention).

Concurrent administration of hydromorphone and mono-amine oxidase inhibitors or within two weeks of discontinuation of their use is contraindicated (see section 4.3).

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of hydromorphone in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Hydromorphone should not be used in pregnancy unless clearly necessary.

Palladone is not recommended during pregnancy and labour due to impaired uterine contractility and the risk of neonatal respiratory depression. Chronic use during pregnancy may lead to withdrawal symptoms in the new-born infant.

Lactation
Hydromorphone is excreted into breast milk in low amounts. Palladone should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

Hydromorphone may impair the ability to drive and use machines. This is particularly likely at the initiation of treatment with hydromorphone, after dose increase or product rotation and if hydromorphone is combined with alcohol or other CNS depressant substances. Patients stabilised on a specific dosage will not necessarily be restricted. Patients should therefore consult with their physician whether driving or the use of machinery is permitted.

4.8 Undesirable effects

The following frequency categories form the basis for classification of the undesirable effects:

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

Immune system disorders:
Very rare: hypersensitivity reactions (including orophyngeal swelling)
Not known: anaphylactic reactions

Metabolism and nutrition disorders
Common: anorexia

Psychiatric disorders:
Common: anxiety, confusional state, insomnia
Uncommon: depression, dysphoria, euphoria, hallucinations, nightmares
Rare: drug dependence, agitation

Nervous system disorders:
Common: dizziness, somnolence
Uncommon: headache, tremor, myoclonus, paraesthesia
Rare: convulsions, sedation
Very rare: hyperalgesia (see section 4.4)

Eye disorders:
Uncommon: miosis, blurred vision

Cardiac disorders:
Uncommon: tachycardia
Rare: bradycardia, palpitations

Vascular disorders:
Common: hypotension

Respiratory, thoracic and mediastinal disorders:
Uncommon: dyspnoe
Rare: respiratory depression, bronchospasm

Gastrointestinal disorders:
Common: constipation, abdominal pain, dry mouth, nausea, vomiting
Uncommon: dyspepsia, diarrhoea, dysgeusia
Very rare: paralytic ileus

Hepato-biliary disorders:
Rare: biliary colic, elevation of pancreatic enzymes
Very rare: hepatic enzymes increased

Skin and subcutaneous tissue disorders:
Common: pruritus, sweating
Uncommon: rash, urticaria
Rare: facial flushing

Renal and urinary disorders:
Common: urinary retention, urgency

Reproduction system and breast disorders:
Uncommon: decreased libido, erectile dysfunction

General disorders and administration site conditions:
Common: asthenic conditions, injection site reactions
Uncommon: drug tolerance, drug withdrawal syndrome*
Very rare: peripheral oedema, injection site induration (particularly after repeated s.c. administration)

*A withdrawal syndrome may occur and include symptoms such as agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal symptoms.

4.9 Overdose

Signs of hydromorphone intoxication and overdose include miosis, bradycardia, respiratory depression, hypotension, somnolence progressing to stupor and coma. Circulatory failure and deepening coma may occur in more severe cases and may lead to a fatal outcome.

In unconscious patients with respiratory arrest intubation and assisted respiration may be required. An opioid antagonist (e.g. naloxone 0.4 mg; in children: naloxone 0.01 mg/kg BW) should be administered intravenously. Individual administration of the antagonist should be repeated at 2 to 3-minute intervals as necessary.
Close monitoring (at least for 24 hours) is required, since the effect of the opioid antagonist is shorter than that of hydromorphone, so that repeated occurrence of the signs of overdose like respiratory insufficiency are to be expected.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: analgesics; opioids; natural opium alkaloid
ATC code: N02A A03.

Hydromorphone is a μ-selective, full opioid agonist. Hydromorphone and related opioids produce their major effects on the central nervous system and the intestine.

The effects are primarily analgesic, anxiolytic, antitussive and sedative. Moreover, mood swings, respiratory depression, reduced gastrointestinal motility, nausea, vomiting and alteration of the endocrine and vegetative nervous system may occur.

Opioids may influence the hypothalamic-pituitary-adrenal or -gonadal axes. The reported changes include an increase in serum prolactin and decreases in plasma cortisol and testosterone. Clinical symptoms resulting from these hormonal changes may become manifest.

Preclinical studies indicate various effects of opioids on components of the immune system. The clinical significance of these findings is unknown.

5.2 Pharmacokinetic properties

The onset of action after intravenous and subcutaneous injection is usually within 5 minutes and 5-10 minutes, respectively. The duration of action is 3-4 hours after intravenous or subcutaneous injection. After epidural administration of 1 mg hydromorphone hydrochloride, a latency of 22.5 ± 6 minutes was observed until full analgesia was achieved. The effect was maintained for 9.8 ± 5.5 hours (n=84 patients aged 22-84).

Hydromorphone hydrochloride crosses the placenta barrier. There are no data available on the excretion of the substance into the breast milk.

Plasma protein binding of hydromorphone is low (< 10 %). This percentage of 2.46 ng/ml remains constant up to very high plasma levels of 81.99 ng/ml, which are only very rarely achieved with very high hydromorphone doses.

Hydromorphone hydrochloride has a relatively high distribution volume of 1.22 ± 0.23 l/kg (C.I.: 90 %: 0.97 – 1.60 l/kg) (n = 6 male subjects), which suggests a pronounced tissue uptake.

The course of the plasma concentration time curves after single administration of hydromorphone hydrochloride 2 mg i.v. or 4 mg oral to 6 healthy volunteers in a randomised cross-over study revealed a relatively short elimination half-life of 2.64 ± 0.88 hours (1.68-3.87 hours)

Hydromorphone is metabolised by direct conjugation or reduction of the keto group with subsequent conjugation. After absorption, hydromorphone is primarily metabolised to hydromorphone-3-glucuronide, hydromorphone-3-glucoside and dihydroisomorphine-6-glucuronide. Smaller portions of the metabolites dihydroisomorphine-6-glucoside, dihydromorphine and dihydroisomorphine have also been found. Hydromorphone is metabolised via the liver; a smaller portion is excreted unchanged via the kidneys.

Hydromorphone metabolites were found in plasma, urine and human hepatocyte test systems. There are no indications to hydromorphone being metabolised in vivo via the cytochrome P 450 enzyme system. In vitro, hydromorphone has but a minor inhibition effect (IC50 > 50 ㎜) on recombinant CYP isoforms, including CYP1A2, 2A6, 2C8, 2D6 und 3A4. Hydromorphone is therefore not expected to inhibit the metabolism of other active substances which metabolise via these CYP isoforms.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

No effects on male or female fertility or sperm parameters were observed in rats at oral hydromorphone doses of 5 mg/kg/day (30 mg/m^2/day, which is 1.4 times higher than the expected human dose on a body surface area basis).

Hydromorphone was not teratogenic in rats and rabbits at doses that caused maternal toxicity. Reduced foetal development was found in rabbits at doses of 50 mg/kg (developmental no-effect level was established at a dose of 25 mg/kg or 380 mg/m^2 at an active substance exposure (AUC) almost four times above the one expected in humans). No evidence of foetal toxicity was observed in rats treated with oral hydromorphone doses as high as 10 mg/kg (308 mg/m^2 with an AUC about 1.8 times above the one expected in humans).

Perinatum and postpartum rat pup (F1) mortality was increased at doses of 2 and 5 mg/kg/day and bodyweights were reduced during lactation period.

Long-term carcinogenicity studies have not been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid anhydrous
Sodium citrate
Sodium chloride
Sodium hydroxide solution (4%) (for pH-adjustment)
Hydrochloric acid 3.6% (for pH-adjustment)
Water for injections

6.2 Incompatibilities

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

6.3 Shelf Life

3 years.

Shelf life after first opening: For immediate use.

Palladone, undiluted or diluted with sodium chloride 9 mg/ml (0.9%) solution for infusion, glucose 50 mg/ml (5%) solution for infusion or water for injections, is physically and chemically stable when in contact with representative brands of polypropylene or polycarbonate syringes, polyethylene or PVC tubing, and PVC or EVA infusion bags, over a 24 hour period at ambient temperature (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 ambient temperature (25°C), unless reconstitution / dilution (etc) has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

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

For further information on use after opening see section 6.6.

6.5 Nature and contents of container

Type 1, clear, neutral glass ampoules in packs of 5 x 1 ml ampoules

6.6 Special precautions for disposal and other handling

No evidence of incompatibility was observed between Palladone undiluted and diluted with sodium chloride 9 mg/ml (0.9%) solution for infusion, glucose 50 mg/ml (5%) solution for infusion or water for injections and representative brands of injectable forms of the following medicinal products, when stored in high and low dose combinations in polypropylene syringes over a 24 hour period at ambient temperature.

Hyoscine butylbromide
Hyoscine hydrobromide
Dexamethasone sodium phosphate
Haloperidol
Midazolam hydrochloride
Metoclopramide hydrochloride
Levomepromazine hydrochloride
Glycopyrronium bromide
Ketamine hydrochloride

Inappropriate handling of the undiluted solution after opening of the original ampoule, or of the diluted solutions may compromise the sterility of the product.

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

7 MARKETING AUTHORISATION HOLDER

Napp Pharmaceuticals Limited
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Cambridge
CB4 0GW
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8 MARKETING AUTHORISATION NUMBER

PA913/15/14

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 31st July 2009

10 DATE OF REVISION OF THE TEXT

November 2010