

## **SUMMARY OF PRODUCT CHARACTERISTICS**

### **1 NAME OF THE MEDICINAL PRODUCT**

Palladone 1.3mg Capsules

### **2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each capsule contains hydromorphone hydrochloride 1.3 mg.

Excipient with known effect:

Each capsule contains 39.35 mg of lactose.

For the full list of excipients, see section 6.1.

### **3 PHARMACEUTICAL FORM**

Capsule, hard.

Hard gelatin capsule with opaque orange, body and clear uncoloured cap, marked HNR 1.3.

### **4 CLINICAL PARTICULARS**

#### **4.1 Therapeutic indications**

For the relief of severe pain in cancer.

Palladone capsules are indicated in adults and children aged 12 years and above.

#### **4.2 Posology and method of administration**

##### Posology

Prior to starting treatment with opioids, a discussion should be held with patients to put in place a strategy for ending treatment with hydromorphone in order to minimise the risk of addiction and drug withdrawal syndrome (see section 4.4).

##### Transferring patients between oral and parenteral hydromorphone

Switching patients from parenteral hydromorphone to oral hydromorphone should be guided by the sensitivity of the individual patient. The oral starting dose should not be overestimated (for oral bioavailability see section 5.2).

#### Adults and children aged 12 years and above

*Palladone* capsules should be used at 4 hourly intervals. The dosage is dependent upon the severity of the pain and the patient's previous history of analgesic requirements. 1.3 mg of hydromorphone has an efficacy approximately equivalent to 10 mg of morphine given orally. A patient presenting with severe pain should normally be started on a dosage of one *Palladone* capsule 4 hourly. Increasing severity of pain may require increased dosage of hydromorphone to achieve the desired relief.

#### Elderly and patients with renal impairment

The elderly and patients with renal impairment should be dose titrated with *Palladone* capsules in order to achieve adequate analgesia. It should be noted, however, that these patients may require a lower dosage to achieve adequate analgesia.

#### Patients with hepatic impairment

Contraindicated.

#### Paediatric population

Not recommended.

#### Method of administration

For oral use.

The capsules can be swallowed whole or opened and their contents sprinkled on to cold soft food.

#### Treatment goals and discontinuation:

Before initiating treatment with *Palladone* capsules, a treatment strategy including treatment duration and treatment goals, and a plan for end of the treatment, should be agreed together with the patient, in accordance with pain management guidelines. During treatment, there should be frequent contact between the physician and the patient to evaluate the need for continued treatment, consider discontinuation and to adjust dosages if needed. When a patient no longer requires therapy with hydromorphone, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal. In absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered (see section 4.4).

#### Duration of treatment:

Hydromorphone should not be used longer than necessary.

### **4.3 Contraindications**

Hydromorphone is contra-indicated in patients with:

- Known hypersensitivity to hydromorphone or any of the excipients (see section 6.1).

- Severe respiratory depression with hypoxia and/or hypercapnia
- Severe chronic obstructive lung disease
- Severe bronchial asthma
- Paralytic ileus
- Acute abdomen
- Coma
- Hepatic impairment
- Concurrent administration of monoamine oxidase inhibitors or within 2 weeks of discontinuation of their use.

#### 4.4 Special warnings and precautions for use

Hydromorphone should be administered with caution in the debilitated elderly and in patients with:

- Severely impaired respiratory function
- Sleep apnoea
- CNS depressants co-administration (see below and section 4.5)
- Head injury, intracranial lesions or increased intracranial pressure, reduced level of consciousness of uncertain origin
- Hypotension with hypovolaemia
- Pancreatitis
- Hypothyroidism
- Toxic psychosis
- Prostatic hypertrophy
- Adrenocortical insufficiency (e.g., Addison's disease)
- Severely impaired renal function
- Severely impaired hepatic function
- Alcoholism
- Delirium tremens
- Convulsive disorders
- Constipation
- Shock or reduced respiratory reserve.

##### Respiratory depression

The major risk of opioid excess is respiratory depression.

Opioids may cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use may increase the risk of CSA in a dose-dependent manner in some patients. Opioids may also cause worsening of pre-existing sleep apnoea (see section 4.8). In patients who present with CSA, consider decreasing the total opioid dosage.

##### Risk from concomitant use of sedative medicines such as benzodiazepines (and other CNS depressants):

Concomitant use of *Palladone* capsules 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 **Palladone** capsules 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).

#### Sleep-related breathing disorders

Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent manner (see section 4.8).

In patients who present with CSA, consider decreasing the total opioid dosage

#### Tolerance and Opioid Use Disorder (abuse and dependence)

Tolerance, physical and/or psychological dependence may develop upon repeated administration of opioids such as hydromorphone.

Repeated use of **Palladone** can lead to Opioid Use Disorder (OUD). A higher dose and longer duration of opioid treatment can increase the risk of developing OUD. Abuse or intentional misuse of **Palladone** may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality disorders).

Before initiating treatment with **Palladone** and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see section 4.2). Before and during treatment the patient should also be informed about the risks and signs of OUD. If these signs occur, patients should be advised to contact their physician.

Patients will require monitoring for signs of drug-seeking behaviour (e.g. too early requests for refills). This includes the review of concomitant opioids and psycho-active drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

**Palladone** capsules should be used with caution pre-operatively and within the first 24 hours post-operatively, particularly following abdominal surgery.

**Palladone** capsules should not be used where there is the possibility of paralytic ileus occurring. Should paralytic ileus be suspected or occur during use, **Palladone** capsules should be discontinued immediately. Patients about to undergo cordotomy or other pain relieving surgical procedures should not receive **Palladone** capsules for 4 hours prior to surgery. If further treatment with **Palladone** capsules is indicated then the dosage should be adjusted to the new post-operative requirement.

### Drug dependence, tolerance and potential for abuse

For all patients, prolonged use of this product may lead to drug dependence (addiction), even at therapeutic doses. The risks are increased in individuals with current or past history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g. major depression).

Additional support and monitoring may be necessary when prescribing for patients at risk of opioid misuse.

A comprehensive patient history should be taken to document concomitant medications, including over-the-counter medicines and medicines obtained on-line, and past and present medical and psychiatric conditions.

Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of pain control as initially experienced. Patients may also supplement their treatment with additional pain relievers. These could be signs that the patient is developing tolerance. The risks of developing tolerance should be explained to the patient.

Overuse or misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed and do not give this medicine to anyone else.

Patients should be closely monitored for signs of misuse, abuse or addiction.

The clinical need for analgesic treatment should be reviewed regularly.

### Drug withdrawal syndrome

Prior to starting treatment with any opioids, a discussion should be held with patients to put in place a withdrawal strategy for ending treatment with hydromorphone.

Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take weeks to months.

The opioid drug withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.

If women take this drug during pregnancy there is a risk that their newborn infants will experience neonatal withdrawal syndrome.

### Hyperalgesia

Hyperalgesia may be diagnosed if the patient on long-term opioid therapy presents with increased pain. This might be qualitatively and anatomically

distinct from pain related to disease progression or to breakthrough pain resulting from development of opioid tolerance. Pain associated with hyperalgesia tends to be more diffuse than the pre-existing pain and less defined in quality. Symptoms of hyperalgesia may resolve with a reduction of opioid dose.

Opioids, such as hydromorphone, may influence the hypothalamic-pituitary-adrenal or –gonadal axes. Some changes that can be seen include an increase in serum prolactin, and decreases in plasma cortisol and testosterone. Clinical symptoms may be manifest from these hormonal changes.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption, should not take this medicine.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

##### Central nervous system (CNS):

The concomitant use of opioids with sedative medicines such as benzodiazepines or other drugs that depress the CNS 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). Drugs which depress the CNS include, but are not limited to: other opioids, anxiolytics, hypnotics and sedatives (including benzodiazepines), anaesthetics (e.g. barbiturates), antiemetics, antidepressants, antipsychotics (e.g. phenothiazines), antihistamines and alcohol. Alcohol may also enhance the pharmacodynamic effects of hydromorphone; concomitant use should be avoided.

The concomitant use of opioids and gabapentinoids (gabapentin and pregabalin) increases the risk of opioid overdose, respiratory depression and death.

Co-administration with monoamine oxidase inhibitors or within two weeks of their discontinuation of their use is contraindicated (see section 4.3).

#### **4.6 Fertility, pregnancy and lactation**

##### Pregnancy

There are no well-controlled studies of hydromorphone in pregnant women. Hydromorphone should not be used in pregnancy unless clearly necessary. **Palladone** capsules are not recommended during pregnancy and labour due to impaired uterine contractility. Regular use in pregnancy may cause drug dependence in the foetus, leading to withdrawal symptoms in the neonate. If opioid use is required for a prolonged period in pregnant women, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Administration during labour may depress respiration in the neonate and an antidote for the child should be readily available.

### Breast-feeding

Administration to nursing women is not recommended as hydromorphone is excreted into breast milk in low amounts and may cause respiratory depression in the infant.

### Fertility

Non clinical toxicology studies in rats have not shown any effects on male or female fertility or sperm parameters.

## **4.7 Effects on ability to drive and use machines**

Hydromorphone may cause drowsiness and patients should not drive or operate machinery if affected.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive.
- Do not drive until you know how the medicine affects you.
- It is an offence to drive while you have this medicine in your body over a specified limit unless you have a defence (called the 'statutory defence').
- This defence applies when:
  - The medicine has been prescribed to treat a medical or dental problem; and
  - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine.
- Please note that it is still an offence to drive if you are unfit because of the medicine (i.e. your ability to drive is being affected)."

Details regarding a new driving offence concerning driving after drugs have been taken in the UK may be found here: <https://www.gov.uk/drug-driving-law>

## **4.8 Undesirable effects**

Hydromorphone may cause constipation, nausea and vomiting. Constipation may be treated with appropriate laxatives. When nausea and vomiting are troublesome *Palladone* capsules can be readily combined with antiemetics.

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

Term	Frequency
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

	<b>Very common</b>	<b>Common</b>	<b>Uncommon</b>	<b>Rare</b>	<b>Very rare</b>	<b>Not known</b>
<b>Immune system disorders</b>						Hypersensitivity (including oropharyngeal swelling); Anaphylactic reactions
<b>Metabolism and nutrition disorders</b>		Decreased appetite				
<b>Psychiatric disorders</b>		Anxiety Confusional state Insomnia	Agitation Depression Euphoric mood Hallucination Nightmares			Drug dependence (see section 4.4) Dysphoria
<b>Nervous system disorders</b>	Dizziness Somnolence	Headache	Myoclonus Paraesthesia Tremor	Sedation Lethargy		Convulsions Dyskinesia Hyperalgesia (see section 4.4) Central sleep apnoea syndrome
<b>Eye disorders</b>			Visual impairment			Miosis
<b>Cardiac disorders</b>				Tachycardia		
<b>Vascular disorders</b>			Hypotension			Flushing
<b>Respiratory, thoracic and mediastinal disorders</b>			Dyspnoea	Respiratory depression		
<b>Gastrointestinal disorders</b>	Constipation Nausea	Abdominal pain Dry mouth Vomiting	Diarrhoea Dysgeusia			Paralytic ileus
<b>Hepatobiliary disorders</b>			Hepatic enzymes increased			
<b>Skin and subcutaneous tissue disorders</b>		Pruritus Hyperhidrosis	Rash			Urticaria
<b>Renal and urinary disorders</b>			Urinary retention			
<b>Reproductive system and breast disorders</b>			Erectile dysfunction			

General disorders and administration site conditions		Asthenia	Drug withdrawal syndrome Fatigue Malaise Peripheral oedema			Drug tolerance Drug withdrawal syndrome neonatal
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### Description of selected adverse reactions

#### Drug dependence

Repeated use of *Palladone* capsules can lead to drug dependence, even at therapeutic doses. The risk of drug dependence may vary depending on a patient's individual risk factors, dosage, and duration of opioid treatment (see 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 via the Yellow Card Scheme at:

[www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard) or search for MHRA Yellow Card in the Google Play or Apple App Store.

#### **4.9 Overdose**

Signs of hydromorphone toxicity and overdose are pin-point pupils, respiratory depression and hypotension. Circulatory failure and somnolence progressing to stupor or deepening coma, pneumonia aspiration, skeletal muscle flaccidity, bradycardia and death may occur in more severe cases. Rhabdomyolysis progressing to renal failure has been reported in opioid overdose.

Toxic leukoencephalopathy has been observed with hydromorphone overdose.

Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.

#### Treatment of overdose:

Primary attention should be given to the establishment of a patent airway and institution of assisted or controlled ventilation.

In the case of massive overdose, administer naloxone intravenously (0.4 to 2 mg for an adult and 0.01 mg/kg body weight for children), if the patient is in a coma or respiratory depression is present. Repeat the dose at 2 minute intervals if there is no response. If repeated doses are required then an infusion of 60% of the initial dose per hour is a useful starting point. A solution of 10 mg made up in 50 ml dextrose will produce 200 micrograms/ml for infusion using an IV pump (dose adjusted to the clinical response). Infusions are not a substitute for frequent review of the patient's clinical state.

Intramuscular naloxone is an alternative in the event IV access is not possible. As the duration of action of naloxone is relatively short, the patient must be carefully monitored until spontaneous respiration is reliably re-established. Naloxone is a competitive antagonist and large doses (4 mg) may be required in seriously poisoned patients. For less severe overdose, administer naloxone 0.2 mg intravenously followed by increments of 0.1 mg every 2 minutes if required.

Naloxone should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to hydromorphone overdose. Naloxone should be administered cautiously to persons who are known, or suspected, to be physically dependent on hydromorphone. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute withdrawal syndrome.

Other supportive measures as indicated by the patient's progress and clinical condition should be considered.

Additional/other considerations:

Consider activated charcoal (50 g for adults, 1 g/kg for children), if a substantial amount has been ingested within 1 hour, provided the airway can be protected.

Gastric contents may need to be emptied as this can be useful in removing unabsorbed drug.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: natural opium alkaloid  
ATC code: N02A A03

Hydromorphone is an opioid agonist with no antagonist activity. Its therapeutic action is mainly analgesic, anxiolytic, antitussive and sedative. The mechanism of action involves CNS opioid receptors for endogenous compounds with opioid-like activity. Hydromorphone and related opioids produce their major effects on the central nervous system and bowel.

The oral analgesic potency ratio of hydromorphone to morphine is approximately 5-10:1.

Endocrine System

See section 4.4.

Other Pharmacologic Effects

In vitro and animal studies indicate various effects of natural opioids, such as morphine, on components of the immune system; the clinical significance of

these findings is unknown. Whether hydromorphone, a semisynthetic opioid, has immunological effects similar to morphine is unknown.

## **5.2 Pharmacokinetic properties**

### Absorption:

Hydromorphone is absorbed from the gastrointestinal tract and undergoes pre-systemic elimination resulting in an oral bioavailability of about 32%.

### Distribution

Plasma protein binding of hydromorphone is low (< 10 %). This percentage remains constant up to very high plasma levels of approximately 80 ng/ml, which are only very rarely achieved with very high hydromorphone doses.

### Metabolism

Hydromorphone is metabolised by direct conjugation or reduction of the keto group with subsequent conjugation. 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.

### Elimination

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 (IC<sub>50</sub> > 50 µM) 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**

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

## **6.1 List of excipients**

Microcrystalline cellulose  
Lactose (anhydrous)

### Capsule shells

Gelatin  
Erythrosine (E127)  
Iron oxide (E172)  
Titanium dioxide (E171)  
Sodium laurilsulfate

Black printing ink  
Shellac  
Propylene glycol  
Iron oxide (E172)

**6.2. Incompatibilities**

None known.

**6.3. Shelf Life**

Two years.

**6.4. Special Precautions for Storage**

Do not store above 25°C. Store in the original package.

**6.5. Nature and Contents of Container**

PVdC coated PVC blisters with aluminium backing foil containing 30, 56 or 60 capsules.

**6.6 Special precautions for disposal**

None stated.

**7 MARKETING AUTHORISATION HOLDER**

Napp Pharmaceuticals Limited  
Cambridge Science Park  
Milton Road  
Cambridge  
CB4 0GW

**8 MARKETING AUTHORISATION NUMBER(S)**

PL 16950/0049

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**10 DATE OF REVISION OF THE TEXT**

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