Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Palladone SR 2 mg prolonged release hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Palladone SR 2 mg capsules contain hydromorphone hydrochloride 2 mg equivalent to 1.78 mg hydromorphone.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged release hard capsule (prolonged-release capsule)

Palladone SR 2 mg prolonged release hard capsules are gelatin capsules with opaque white bodies and opaque yellow caps, marked HCR2, containing white to off-white spherical pellets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the relief of severe pain.

4.2 Posology and method of administration

Posology

Adults and adolescents over 12 years:
Palladone SR capsules should be administered at 12-hourly intervals. The dosage is dependent upon the severity of the pain and the patient's previous history of analgesic requirements. 4 mg of hydromorphone hydrochloride has an analgesic efficacy equivalent to 30 mg of morphine sulphate given orally. 2 mg, 4 mg, 8 mg, 16 mg and 24 mg capsules are available.

Treatment should normally be started at a dosage of 4 mg prolonged release hydromorphone hydrochloride 12-hourly. Increasing severity of pain will require an increased dosage of hydromorphone hydrochloride prolonged release products alone or in combination with immediate release hydromorphone product to achieve the desired relief.

Patients who are not currently receiving opioids should be titrated with immediate release hydromorphone hydrochloride initially, prior to changing to Palladone SR capsules.

Transferring patients between oral and parental 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).

Paediatric population
Not recommended for use in children under 12 years.

Elderly
As with adults, the elderly should be dose titrated with Palladone SR capsules in order to achieve adequate analgesia. It should be noted however, that the elderly may require a lower dosage than adults to achieve adequate analgesia.

Patients with renal and hepatic impairment
These patients may require lower doses than other patient groups to achieve pain control. Patients should be carefully titrated to clinical effect.

Method of administration

Oral use.

The capsules can be swallowed whole or opened and their contents sprinkled on to cold soft food. The capsule contents should never be crushed or injected as this may lead to a rapid release and absorption of a potentially fatal dose of hydromorphone.

Treatment goals and discontinuation

Before initiating treatment with ***Palladone SR***, 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 products are contraindicated in patients with:

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Severe respiratory depression with hypoxia and/or hypercapnia
- Severe chronic obstructive lung disease
- Severe bronchial asthma
- Paralytic ileus
- Acute abdomen
- Coma
- Concurrent administration of monoamine oxidase inhibitors or within 2 weeks of discontinuation of their use.

Palladone SR capsules are not recommended for preoperative use or within the first 24 hours postoperatively. After this time, they should be used with caution particularly following abdominal surgery.

4.4 Special warnings and precautions for use

The primary risk of opioid excess is respiratory depression.

Hydromorphone has to be administered with caution in patients with:

- Severely impaired respiratory function
- Sleep apnoea
- CNS depressants co-administration (see below and section 4.5)
- Tolerance, physical dependence and withdrawal (see below)
- Chronic obstructive pulmonary disease
- Reduced respiratory reserve
- Psychological dependence [addiction], abuse profile and history of substance and/or alcohol abuse (see below)
- Debilitated elderly
- Head injury, intracranial lesions or increased intracranial pressure, reduced level of consciousness of uncertain origin (due to the risk of opioids to cause increased intracranial pressure)
- Hypotension with hypovolaemia
- Pancreatitis
- Hypothyroidism
- Toxic psychosis
- Prostatic hypertrophy
- Biliary tract diseases
- Biliary or ureteric colic
- Adrenocortical insufficiency (e.g., Addison's disease)

- Severely impaired renal function
- Severely impaired hepatic function
- Alcoholism
- Delirium tremens
- Convulsive disorders
- Pre-existing constipation
- Obstructive or inflammatory bowel disordersIn all these patients, reduced dosage may be advisable.

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.

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs:

Concomitant use of ***Palladone SR*** capsules and sedative medicines such as benzodiazepines or related drugs may result in profound 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 SR*** 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).

Tolerance and Opioid Use Disorder (abuse and dependence)
Tolerance and physical and/or psychological dependence may develop upon repeated administration of opioids sush as hydromorphone.

Repeated use of ***Palladone SR*** 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 SR*** capsules 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 SR*** 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.

The patient may develop tolerance to the drug with chronic use and require progressively higher doses to maintain pain control. There may also be cross-tolerance with other opioids. Prolonged use of this product 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 dose gradually to prevent symptoms of withdrawal.

The content (pellets) of the prolonged release capsules must be swallowed whole and not broken, chewed or crushed. The administration of broken, chewed or crushed hydromorphone granules/pellets leads to a rapid release and absorption of a potentially fatal dose of hydromorphone (see section 4.9).

Concomitant use of alcohol and ***Palladone SR*** capsules may increase the undesirable effects of ***Palladone SR*** capsules; concomitant use should be avoided.

Abuse of oral dosage forms by parenteral administration can be expected to result in serious adverse events, which may be fatal.

PalladoneSR capsules should not be used where there is the possibility of paralytic ileus occurring. Should paralytic ileus be suspected or occur during use, hydromorphone treatment must be discontinued immediately.

Patients about to undergo additional pain relieving procedures (e.g. surgery, plexus blockade) should not receive hydromorphone for 12 hours prior to the intervention. If further treatment with ***PalladoneSR*** is indicated then the dosage should be adjusted to the new post-operative requirement. ***PalladoneSR*** is not recommended for preoperative use or within the first 24 hours postoperatively.

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

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 manifest from these hormonal changes.

Caution should be exercised when treating patients with pre-existing constipation. Appropriate use of laxative treatment should be considered.

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

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

Central nervous system (CNS):
The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs 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 (incl. benzodiazepines), antipsychotics, anaesthetics (e.g. barbiturates), antiemetics, antidepressants, antihistaminic drugs, phenothiazines and alcohol.

Alcohol may also enhance the pharmacodynamic effects of ***Palladone SR*** capsules; 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.

Concurrent administration of hydromorphone and mono-amine oxidase inhibitors or within two weeks of discontinuation of their use must be avoided. No formal studies of drug interaction with ***Palladone SR*** capsules have been performed.

4.6 Fertility, pregnancy and lactation

Palladone SR capsules are not recommended in pregnancy or the breast-feeding mother.

Pregnancy
No clinical data on exposed pregnancies are available.

Animal studies revealed no teratogenic effects at doses that give exposure greater than those expected in humans (see Section 5.3).

Palladone SR capsules should not be used during pregnancy and labour due to impaired uterine contractility and the risk of neonatal respiratory depression. Prolonged use of hydromorphone during pregnancy can result in neonatal withdrawal syndrome.

Lactation

No data are available on the use of hydromorphone during lactation. ***Palladone SR*** capsules should therefore not be used in breast-feeding mothers, otherwise breast-feeding should be stopped.

Fertility

Animal studies revealed no evidence of an effect on fertility or reproductive parameters at oral doses as high as 5 mg/kg/day. Peri-natal toxicity was noted in rats treated with 2 and 5 mg/kg/day.

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 CNS depressant agents. Patients stabilised on a specific dosage will not necessarily be restricted. Therefore, patients should consult with their physician as to 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: ≥1/1000 to <1/100
Rare: ≥1/10000 to <1/1000
Very rare: <1/10000
Not known: cannot be estimated from the available data

	Very common	Common	Uncommon	Rare	Not known
Immune system disorders					Anaphylactic reactions Hypersensitivity (including oropharyngeal swelling)
Metabolism and nutrition disorders		Decreased appetite			
Psychiatric disorders		Anxiety Confusional state Insomnia	Agitation Depression Euphoric mood Hallucination Nightmares	Aggression	Drug dependence (see section 4.4) Dysphoria
Nervous system disorders	Dizziness Somnolence	Headache	Tremor Myoclonus Paraesthesia	Sedation Lethargy	Convulsions Dyskinesia Hyperalgesia Central sleep apnoea syndrome (see section 4.4)
Eye disorders			Visual impairment		Miosis
Cardiac disorders				Bradycardia Palpitations Tachycardia	
Vascular disorders			Hypotension		Flushing
Respiratory, thoracic and mediastinal disorders			Dyspnoea	Respiratory depression Bronchospasm	

Gastrointestinal disorders	Constipation Nausea	Abdominal pain Dry mouth Vomiting	Dyspepsia Diarrhoea Dysgeusia		Paralytic ileus
Hepatobiliary disorders			Hepatic enzymes increased	Elevation of pancreatic enzymes	
Skin and subcutaneous tissue disorders		Pruritus Hyperhidrosis	Rash		Urticaria
Renal and urinary disorders		Urgency	Urinary retention		
Reproductive system and breast disorders			Decreased libido Erectile dysfunction		
General disorders and administration site conditions		Asthenia	Drug withdrawal syndrome* Fatigue Malaise Peripheral oedema		Drug tolerance Drug withdrawal syndrome neonatal

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

Drug dependence

Repeated use of ***Palladone SR*** 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 HPRA Pharmacovigilance,
Website: www.hpra.ie.

4.9 Overdose

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

Toxic leukoencephalopathy has been observed with hydromorphone overdose.

In unconscious patients with respiratory arrest, intubation and assisted respiration may be required. Naloxone 0.8 mg should be administered intravenously. This should be repeated at 2-3 minute intervals as necessary, or by an infusion of 2 mg in 500 ml of sodium chloride solution or 5% w/v glucose solution (0.004 mg ml^{-1}). The infusion should be run at a rate relative to the previous bolus doses administered and should be in accordance with the patient's response. Respiration should be assisted if necessary. Fluid and electrolyte levels should be maintained. 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. Controlled release delivery systems may have a prolonged action, which should be considered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Opioid analgesic; natural opium alkaloid.
ATC code: N02A A03.

Like morphine, hydromorphone is an opioid agonist with no antagonist activity. The pharmacological actions of hydromorphone and morphine do not differ significantly. Hydromorphone and related opioids produce their major effects on the central nervous system and bowel. Its therapeutic action is mainly 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.
There have been no long term clinical studies with ***Palladone SR*** capsules.

Endocrine System
See section 4.4.

Hepatobiliary System
Opioids may induce biliary spasm.

Other Pharmacologic System
In vitro animal studies indicate various effects of natural opioids, such as morphone, on components of the immune system; the clinical significance of these findings is unknown. Whether hydromorphone, a semisynthetic opioid, has immunological effects similar to natural opioids 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% (range 17-62%).

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.

Biotransformation
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 (IC50 > 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

Reproductive and Developmental Toxicity
No effects have been observed on male or female fertility or sperm parameters in rats at oral hydromorphone doses as high as 5 mg/kg/day (30 mg/m2/day or 1.4 times the expected human dose on a surface area basis).

Hydromorphone was not teratogenic in pregnant rats nor rabbits given oral doses during the major period of organ development. Reduced foetal development was observed in rabbits at 50 mg/kg (the developmental no-effect level dose of 25 mg/kg or 380 mg/m2 at a drug exposure, AUC, approximately 4 times that expected in humans). No evidence of foetal toxicity was observed in rats at oral hydromorphone doses as high as 10 mg/kg (308 mg/m2 at an AUC approximately 1.8 times that expected in humans). Evidence of a teratogenic effect in mice and hamsters has been reported in the literature.

A pre- and post-natal study in rats showed that there was an increase in pup mortality at 2 and 5 mg/kg/day and reduced body weight gain in the early postnatal period, associated with maternal toxicity. No effects on continued pup development or reproductive performance were observed.

Carcinogenicity
Hydromorphone was non-genotoxic in a bacterial mutation test, in the *in vitro* human lymphocyte chromosome aberration assay and *in vivo* mouse micronucleus assay. But positive in mouse lymphoma assay with metabolic activation. Similar findings have been reported with other opioid analgesics.

Long term carcinogenicity studies have not been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents
Microcrystalline cellulose

Hypromellose
Ethylcellulose
Colloidal anhydrous silica
Dibutyl sebacate

Capsule shells
Gelatin
Sodium laurilsulfate

In addition the capsule shells contain the following colours:
2 mg Quinoline yellow (E104)
4 mg Erythrosine (E127), Indigo Carmine (E132)
8 mg Erythrosine (E127)
16 mg Iron Oxide (E172)
24 mg Indigo Carmine (E132)

Black printing ink
Shellac
Propylene glycol
Iron oxide (E172)

6.2 Incompatibilities

Not applicable.

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 /PVC blister with aluminium backing foil, containing 30, 56, 60 or 98 capsules.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Mundipharma Pharmaceuticals Limited
United Drug House
Magna Drive Magna Business Park
Citywest Road
Dublin 24
D24 XKE5
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1688/007/007

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 07 December 1995

Date of last renewal: 07 December 2005

10 DATE OF REVISION OF THE TEXT

December 2025