

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Palladone SR 16 mg Prolonged-release Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged release capsule, hard, contains hydromorphone hydrochloride 16 mg equivalent to 14.24 mg hydromorphone.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release Capsule, hard (Prolonged-release Capsule)

Gelatin capsules with clear uncoloured bodies and opaque brown caps marked HCR16 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

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.

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.

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.

4.3 Contraindications

Hypersensitivity to hydromorphone or to any of the excipients listed in section 6.1. Significant respiratory depression with hypoxia or elevated carbon dioxide levels in the blood, severe chronic obstructive airways disease, coma, acute abdomen, paralytic ileus, 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 major risk of opioid excess is respiratory depression. Use with caution in opioid dependent patients and 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, diseases of the biliary tract, biliary or ureteric colic, pancreatitis, obstructive and inflammatory bowel disorders, prostatic hypertrophy, adrenocortical insufficiency (e.g. Addison's disease), hypothyroidism, chronic obstructive airways disease, reduced respiratory reserve, in the debilitated, elderly and in patients with severely impaired renal or hepatic function (see Section 4.2). In patients in whom caution is required, a reduced dosage may be advisable.

Patients 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. Hydromorphone has an abuse profile similar to other strong opioid agonists and 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 hydromorphone. **Palladone SR** capsules, like all opioids, should be used with particular care in patients with a history of alcohol and drug abuse.

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 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.

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

Palladone SR 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 **Palladone SR** is indicated then the dosage should be adjusted to the new post-operative requirement.

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.

4.5 Interaction with other medicinal products and other forms of interaction

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

Alcohol may also enhance the pharmacodynamic effects of Palladone SR capsules; concomitant use should be avoided.

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). 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.

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.

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 for 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	<u>Very rare</u>	Not known
Immune system disorders	-	-	-	-	-	Anaphylactic reactions Hypersensitivity reactions (including oropharyngeal

						swelling)
Metabolism and nutrition disorders	-	Decreased appetite	-	-	-	-
Psychiatric disorders	-	Anxiety Confusional state Insomnia	Agitation Depression Euphoric mood Hallucination Nightmares	Aggression -	-	Drug dependence Dysphoria
Nervous system disorders	Dizziness Somnolence	Headache	Tremor Myoclonus Paraesthesia	Sedation Lethargy	-	Convulsions Dyskinesia Hyperalgesia (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 Neonatal drug withdrawal syndrome

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

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, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@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.

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 patients 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 a μ 1 selective full opioid agonist. 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. 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 induce biliary spasm. There have been no long term clinical studies with **Palladone** SR capsules.

Endocrine System

Opioids 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.

Hepatobiliary System

Opioids may induce biliary spasm

Other Pharmacologic System

Preclinical studies indicate various effects of opioids 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

Hydromorphone is absorbed from the gastrointestinal tract and undergoes pre-systemic elimination resulting in an oral

bioavailability of about 32% (range 17-62%). It is metabolised and excreted in the urine mainly as conjugated hydromorphone and with smaller amounts of unchanged hydromorphone, dihydroisomorphine and dihydromorphine.

5.3 Preclinical safety data

Reproductive and Development 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 the *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
Iron Oxide (E172)
Titanium Dioxide (E171)
Sodium Laurilsulfate

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 blisters with aluminium backing foil containing 28, 30, 56, 60 or 98 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Mundipharma Pharmaceuticals Limited
Millbank House
Arkle Road
Sandyford
Dublin 18
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 1688/007/010

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 02 March 1993

Date of last renewal: 18 August 2009

10 DATE OF REVISION OF THE TEXT

May 2017