Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Hydromorphone-HCl Krugmann 1.3 mg capsules, hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Hydromorphone-HCl Krugmann 1.3 mg capsules, hard contain hydromorphone hydrochloride 1.30 mg equivalent to 1.16 mg hydromorphone.

Excipients with known effect:
Each Hydromorphone-HCl Krugmann 1.3 mg capsule, hard contains 39.35 mg of lactose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard (capsule).

Hydromorphone-HCl Krugmann capsules, hard 1.3 mg are gelatin capsules with clear uncoloured caps and opaque orange bodies, containing white to off-white spherical pellets. The capsule is marked HNR 1.3.

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.

Posology

Adults and adolescents over 12 years:
The dosage is dependent upon the severity of the pain and the patient's previous history of analgesic requirements. 1.3 mg of hydromorphone hydrochloride has an efficacy equivalent to 10 mg of morphine sulphate given orally. 1.3 mg and 2.6 mg capsules are available. Treatment should normally be started at a dosage of 1.3 mg or 2.6 mg hydromorphone hydrochloride 4 hourly. Increasing severity of pain will require increased dosage of hydromorphone using 1.3 mg and 2.6 mg capsules alone or in combination with prolonged release hydromorphone products to achieve the desired relief.

Elderly
As with adults, the elderly should be dose-titrated with Hydromorphone-HCl Krugmann hardcapsules 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.

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

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 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. 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.

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs:
Concomitant use of Hydromorphone-HCl Krugmann hard 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 Hydromorphone-HCl Krugmann hard 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).

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. Hydromorphone 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. Hydromorphone-HCl Krugmann hard capsules should be used with particular care in patients with a history of alcohol and drug abuse.

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.

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.

Hydromorphone-HCl Krugmann hard 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.

Hydromorphone-HCl Krugmann hard capsules should be used with caution preoperatively and within 24 hours postoperatively. After this time, they should be used with caution particularly following abdominal surgery.

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 Hydromorphone-HCl Krugmann 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.

This medicinal product contains lactose. 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 interactions

Sedative medicines such as benzodiazepines or related drugs:
The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of respiratory depression, profound sedation, coma and death because of additive CNS depressant effect. Drugs which depress the CNS include, but are not limited to: tranquillisers, anaesthetics (e.g. barbiturates), hypnotics and sedatives (incl. benzodiazepines), antipsychotics, antidepressants, antiemetics, antihistaminic drugs and other opioids, phenothiazines and alcohol. The dose and duration of concomitant use should be limited (see section 4.4).

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 Hydromorphone-HCl Krugmann hard capsules have been performed.

4.6 Fertility, pregnancy and lactation

Hydromorphone-HCl Krugmann hard capsules are not recommended in pregnancy or in 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.

Hydromorphone-HCl Krugmann hard 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. Hydromorphone-HCl Krugmann hard 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 alcohol or other 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 reactions (including oropharyngeal swelling)
Metabolism and nutrition disorders		Decreased appetite			
Psychiatric disorders		Anxiety Confusional state Insomnia	Agitation Depression Euphoric moodHallucination 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		

	Very common	Common	Uncommon	Rare	Not known
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, 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.

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 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Like morphine, hydromorphone is a micro 1 selective full opioid agonist. The pharmaceutical 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.

There have been no long term clinical studies with Hydromorphone-HCl Krugmann hard capsules.

Endocrine System
See section 4.4.

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 a mean oral bioavailability of about 32 % (range 17 – 62%). It is metabolised and excreted in the urine mainly as conjugated hydromorphone, dihydroisomorphine and dihydromorphine.

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/m^2/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/m^2 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/m^2 at an AUC approximately 1.8 times that expected in humans). Evidence of a teratogenic effect in miceand hamstershas 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 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
Lactose anhydrous

Capsule shells:
Gelatin
Erythrosine (E127)
Iron oxide yellow (E172)
Titanium dioxide (E171)
Sodium laurilsulfate

Black printing ink containing:
Shellac
Propylene glycol
Iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 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

PVC/PVdC blister packs with aluminium backing foil containing 20, 28, 30, 50, 56, 60, 98 or 100 capsules.
Hospital pack of 10 ´10 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

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

7 MARKETING AUTHORISATION HOLDER

Mundipharma Pharmaceuticals Limited
Millbank House
Arkle Road
Sandyford
Dublin 18
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1688/022/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17th September 2021

10 DATE OF REVISION OF THE TEXT