Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Hydromorphone Hydrochloride 20 mg/ml Solution for Injection / Concentrate for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1ml ampoule contains 20mg Hydromorphone Hydrochloride.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection
Concentrate for solution for infusion
A clear colourless solution for injection in Type I glass ampoules.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the relief of severe pain in cancer.

Hydromorphone Hydrochloride 20 mg/ml Solution for Injection / Concentrate for Solution for Infusion is indicated in adults and adolescents aged >12 years.

4.2 Posology and method of administration

Posology
The dosing of Hydromorphone Hydrochloride 20 mg/ml Solution for Injection / Concentrate for Solution for Infusion 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 the dose to be administered should be sufficient to achieve appropriate analgesia, the aim should also be to keep the dose as small as possible in the individual case.

Hydromorphone Hydrochloride 20 mg/ml Solution for Injection / Concentrate for Solution for Infusion 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.

Hydromorphone Hydrochloride 20 mg/ml Solution for Injection / Concentrate for Solution for Infusion is not suitable for initial opioid therapy. Higher strengths may only be used as individual doses in patients who have no longer sufficiently responded to lower doses of hydromorphone preparations or comparably strong analgesics within the scope of chronic pain therapy.

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 5-10min.	
Children (<12years)	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.

Paediatric population
Hydromorphone hydrochloride is not recommended for use in children under 12 years of age as the safety and efficacy has not yet been established. No data are available.

Elderly
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).

Method of administration
Subcutaneous/Intravenous injection or infusion
The medicinal product is to be visually inspected prior to use. Only clear solutions free from particles should be used.
After opening, this medicinal product should be used immediately (please refer to section 6.3).
For instructions on dilution of the medicinal product before administration, see section 6.6.

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 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 debilitated, elderly patients and in patients with severely impaired renal or hepatic function (see Section 4.2). In 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 (and other CNS depressants)

Concomitant use of Hydromorphone hydrochloride injection 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 Hydromorphone hydrochloride injection 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, physical and psychological dependence, and opioid use disorder (OUD) may develop upon repeated administration of opioids.
Abuse or intentional misuse of [product name] 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).
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 Hydromorphone hydrochloride injection 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 Hydromorphone hydrochloride injection 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.

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

Hydromorphone hydrochloride injection 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.

Hydromorphone hydrochloride injection 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 Hydromorphone hydrochloride injection is indicated, the dosage should be adjusted to the post-operative requirement.

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.

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.

Hydromorphone Injection contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per daily dose, that is to say 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 other 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 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.

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 well-controlled studies of hydromorphone in pregnant women.
Hydromorphone should not be used in pregnancy unless clearly necessary.
Hydromorphone hydrochloride injection is not recommended 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.

Breast-feeding
Hydromorphone is excreted into breast milk in low amounts. Hydromorphone hydrochloride injection should not be used during breastfeeding.

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 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

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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	Frequency cannot be estimated from the available data

Immune system disorders:
Not known: hypersensitivity reactions (including oropharyngeal swelling) anaphylactic reactions

Metabolism and nutrition disorders
Common: decreased appetite

Psychiatric disorders:
Common: anxiety, confusional state, insomnia
Uncommon: agitation, depression, euphoric mood, hallucinations, nightmares
Not known: drug dependence, dysphoria

Nervous system disorders:
Very common: dizziness, somnolence
Common: headache
Uncommon: tremor, myoclonus, paraesthesia
Rare: sedation, lethargy

Not known: convulsions, dyskinesia, hyperalgesia (see section 4.4), Central sleep apnoea syndrome

Eye disorders:
Uncommon: visual impairment
Not known: miosis

Cardiac disorders:
Rare: bradycardia, palpitations, tachycardia
Vascular disorders:
Uncommon: hypotension
Not known: flushing

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

Gastrointestinal disorders:
Very common: constipation, nausea
Common: abdominal pain, dry mouth, vomiting
Uncommon: dyspepsia, diarrhoea, dysgeusia
Not known: paralytic ileus

Hepato-biliary disorders:
Uncommon: hepatic enzymes increased
Rare: elevation of pancreatic enzymes

Skin and subcutaneous tissue disorders:
Common: pruritus, hyperhidrosis
Uncommon: rash
Not known: urticaria

Renal and urinary disorders:
Common: urinary urgency
Uncommon: urinary retention

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

General disorders and administration site conditions:
Common: asthenia, injection site reactions
Uncommon: drug withdrawal syndrome*, fatigue, malaise, peripheral oedema
Very rare: injection site induration (particularly after repeated s.c. administration)
Not known: 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.

Paediatric population
For infants born to mothers receiving hydromorphone see section 4.6.

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

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

Management
In unconscious patients with respiratory arrest intubation and assisted respiration may be required. An opioid antagonist (e.g. naloxone 0.4 mg) 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.

Endocrine System
See section 4.4.

Other Pharmacological Effects
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

Distribution
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. According to published data, hydromorphone is excreted into breast milk at low amounts.

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 halflife of 2.64 ± 0.88 hours (1.68-3.87 hours)

Biotransformation
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.

Elimination
Hydromorphone metabolites were found in plasma, urine and human hepatocyte test systems. There are no indications of hydromorphone being metabolised in vivo via the cytochrome P 450 enzyme system. In vitro, hydromorphone has 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

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/m2/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/m2 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/m2 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

Sodium citrate
Citric acid monohydrate
Water for injections

6.2 Incompatibilities

Incompatible with minocycline and tetracycline solutions resulting in a colour change to light green, whilst cloudiness and precipitation result when hydromorphone is mixed with sodium thiopental. Mixtures with dexamethasone sodium phosphate, sodium bicarbonate and thiopental sodium exhibit a concentration dependent incompatibility and instability.

6.3 Shelf life

Unopened: 3 years.
The product should be used immediately after opening.

6.4 Special precautions for storage

Do not store above 25°C. Keep container in the outer carton in order to protect from light.

6.5 Nature and contents of container

Clear colourless Type 1 glass ampoules packed in cardboard cartons.
Pack size: 10 x 1ml ampoules.

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

Hydromorphone Injection must be diluted prior to administration by intravenous infusion. The following infusion fluids may be used: 5 % Dextrose in Water, 0.9% Sodium Chloride, Ringers Solution and Water for Injections.
For single use only.
Discard any unused contents.

7 MARKETING AUTHORISATION HOLDER

Ethypharm
194 Bureaux de la Colline - Bâtiment D
92213 Saint-Cloud Cedex
France

8 MARKETING AUTHORISATION NUMBER

PA0549/030/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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