SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Hydofon 2 mg/ml solution for injection/infusion
Hydofon 10 mg/ml solution for injection/infusion
Hydofon 20 mg/ml solution for injection/infusion
Hydofon 50 mg/ml solution for injection/infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

<Product name> 2 mg/ml solution for injection/infusion
Each 1 ml ampoule contains 2 mg hydromorphone hydrochloride (corresponding to 1.77 mg hydromorphone).
Excipient with known effect: 1 ml contains 0.153 mmol of sodium (3.52 mg/ml of sodium)

<Product name> 10 mg/ml solution for injection/ infusion
Each 1 ml ampoule contains 10 mg hydromorphone hydrochloride (corresponding to 8.87 mg hydromorphone).
Each 10 ml ampoule contains 100 mg hydromorphone hydrochloride (corresponding to 88.7 mg hydromorphone).
Excipient with known effect: 1 ml contains 0.128 mmol of sodium (2.93 mg/ml of sodium)

<Product name> 20 mg/ml solution for injection/ infusion
Each 1 ml ampoule contains 20 mg hydromorphone hydrochloride (corresponding to 17.73 mg hydromorphone).
Excipient with known effect: 1 ml contains 0.107 mmol of sodium (2.46 mg/ml of sodium)

<Product name> 50 mg/ml solution for injection/ infusion
Each 1 ml ampoule contains 50 mg hydromorphone hydrochloride (corresponding to 44.33 mg hydromorphone).
Excipient with known effect: 1 ml contains 0.041 mmol of sodium (0.94 mg/ml of sodium)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection/infusion.
Clear, colourless to pale yellow solution with a pH of 3.5 – 4.5.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of severe pain in adults and adolescents over 12 years of age.

4.2 Posology and method of administration

Posology

The dosing of <Product name> has to be adjusted to the patients' severity of pain and to their individual response.

It is recommended to start with the lower doses and increase the dose until the optimal analgesic effect is achieved at the lowest possible dose.

<Product name> 10 mg/ml [20 mg/ml mg and 50 mg/ml] is not suitable for initial opioid therapy. These higher dosage forms may only be used as individual doses in patients who have no longer sufficiently responded to lower doses of hydromorphone preparations (<Product name> 2 mg/ml) or comparably strong analgesics within the scope of chronic pain therapy. The reservoir of a pain pump can also be filled with individual doses of 10 mg, 20 mg or 50 mg as the dose control is secured by the pump calibration.

<Product name> 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.

Age	**Method of administration**	**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 and 0.004 mg/kg bodyweight/h, resp.
	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 and 0.004 mg/kg bodyweight/h, resp.
	PCA (s.c. and i.v.)	0.2 mg bolus, stop interval 5-10 min.	
Children (< 12 years)	Not recommended.		

Transferring patients between oral and parenteral hydromorphone:

The daily dose should be based on the following ratio: 3 mg of oral hydromorphone is equivalent to 1 mg of parenterally 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.

Elderly patients

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).

Paediatric population

<Product name> *2 mg/ml [10 mg/ml, 20 mg/ml, 50 mg/ml]* is not recommended for use in children under 12 years of age due to insufficient data on safety and efficacy.

Method of administration:
Intravenous injection or infusion.
Subcutaneous injection or infusion.
<Product name> is intended for single use only.
The medicinal product is to be visually inspected prior to use. Only clear solutions free from visible 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

Hydromorphone products are contraindicated in patients with:

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- significant respiratory depression with hypoxia or elevated carbon dioxide levels in the blood (hypercapnia)
- severe chronic obstructive pulmonary disease
- severe bronchial asthma
- 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

Hydromorphone should be used with caution in patients with

- severely impaired respiratory function
- sleep apnoea
- CNS depressants co-administration (see below and section 4.5)
- psychological dependence (addiction), addiction profile and history of alcohol or drug abuse (see below)
- tolerance, physical dependence and withdrawal (see below)
- head injury (due to the risk of increased intracranial pressure), reduced level of consciousness of uncertain origin
- convulsive disorders
- alcoholism
- delirium tremens
- toxic psychosis
- hypotension with hypovolaemia
- biliary tract diseases
- biliary or ureteric colic
- pancreatitis
- obstructive or inflammatory bowel disorders
- constipation
- prostatic hypertrophy
- adrenocortical insufficiency (e.g. Addison’s disease)
- hypothyroidism
- chronic obstructive pulmonary disease
- reduced respiratory reserve
- in children under 12 years
- 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.

Respiratory Depression
The major risk of opioid excess is respiratory depression.

Sleep-related breathing disorders
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 (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 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 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.

The patient may develop tolerance to the drug 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 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.

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.

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

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

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.

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.

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 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 antiparkinson 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 mono-amine oxidase inhibitors is contraindicated (see section 4.3).

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of hydromorphone in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Prolonged use of hydromorphone during pregnancy can result in neotanal withdrawal syndrome. Hydromorphone should not be used in pregnancy unless clearly necessary.

<Product name> is not recommended during labour due to impaired uterine contractility and the risk of neonatal respiratory depression.

Lactation
Hydromorphone is excreted into breast milk in low amounts. <Product name> should not be used during breast-feeding.

Fertility

There are no human data on the effect of hydromorphone on fertility. Non clinical toxicology studies in rats have not shown any effects on male or female fertility or sperm parameters (see section 5.3).

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

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

Very common	≥ 1/10
Common	≥ 1/100 to < 1/10
Uncommon	≥ 1/1.000 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

Adverse reactions by system organ class and frequency						
	Very common	Common	Uncommon	Rare	Very rare	Not known
Immune system disorders						ana-phylactic reactions, hyper-sensitivity reactions (including oro pharyngeal swelling)
Metabolism and nutrition disorders		decreased appetite				
Psychiatric disorders		anxiety, confusional state, insomnia	agitation, depression, euphoric mood, halluci-nations, nightmares			drug dependence (see Section 4.4), dysphoria
Nervous system disorders	dizziness, som-nolence	headache	tremor, myoclonus, para-	sedation, lethargy		con-vulsions,

			esthesia			dyskinesia, hyper-algesia, central sleep apnoea syndrome (see section 4.4)
Eye disorders			visual impairment			miosis
Cardiac disorders				tachy-cardia, brady-cardia, palpitations		
Vascular disorders			hypo-tension			flushing
Respira-tory, thoracic and mediastinal disorders			dyspnoea	respiratory de-pression, broncho-spasm		
Gastro-intestinal disorders	consti-pation, nausea	dry mouth, vomiting, abdo-minal pain	dyspepsia, diarrhoea, dysgeusia			para-lytic ileus
Hepato-biliary disorders			hepatic enzymes increased	elevation of pancreatic enzymes		
Skin and subcutaneous tissue disorders		pruritus, hyper-hidrosis	rash	facial flushing		urticaria
Renal and urinary disorders		urinary urgency	urinary retention			
Re-production system and breast disorders			decreased libido, erectile dysfunction			
General disorders and administration site conditions		asthenia, injection site reactions	drug withdrawal syndrome*, fatigue, malaise, peripheral oedema		injection site induration (particular-ly after repeated s.c. administration)	drug tolerance, neonatal 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 the national reporting system listed in Appendix V.*

4.9 Overdose

Signs of hydromorphone intoxication and overdose include miosis, bradycardia, respiratory depression, hypotension, somnolence progressing to stupor and coma. A combination of consciousness disorders and vomiting can lead to gastric contents, or other solid material being inhaled. This may lead to aspiration pneumonia. 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. An opioid antagonist (e.g. naloxone 0.4 mg; in children: naloxone 0.01 mg/kg BW) 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

Mechanism of action
Hydromorphone is a μ-selective, full opioid agonist. Hydromorphone and related opioids produce their major effects on the central nervous system and the intestine.

Clinical efficacy and safety
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.

Hepato-biliary system
Opioids may induce convulsions of the bile ducts.

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

Absorption

The onset of action after intravenous injection is usually within 5 minutes, and after subcutaneous injection within 5-10 minutes. 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).

Distribution

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 half-life of 2.64 ± 0.88 hours (1.68-3.87 hours).

Hydromorphone crosses the placenta barrier. Hydromorphone is excreted into breast milk in low amounts.

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 to hydromorphone being metabolised in vivo via the cytochrome P 450 enzyme system. In vitro, hydromorphone has a minor inhibition effect (IC_{50} > 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.

Reproductive and developmental toxicology

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/m^2/day, which is 1.4 times higher than the expected human dose on a body surface area basis).

Hydromorphone, which was administered orally during the main period of organ development, was not teratogenic in pregnant rats or rabbits. 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).

There is evidence in the literature of the teratogenic effects of hydromorphone in mice and hamsters.

In a pre-and a postnatal study in rats there was an increase in rat pup (F1) mortality at doses of 2 and 5 mg/kg/day (which is approximately 0.6 and 1.4 times higher, respectively, than the expected human dose on a body surface area basis) and a reduced bodyweight gain in the early postnatal period, associated with maternal toxicity.

No effects on further development or reproducibility were observed.

Carcinogenicity
Long-term carcinogenicity studies have not been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium citrate
Citric acid monohydrate
Water for injections

6.2 Incompatibilities
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Shelf life of unopened ampoules:
3 years

Shelf life after first opening:
For immediate use.

Chemical and physical in-use stability has been demonstrated for 7 days at 5°C, and for 48 hours at 25°C and 37°C, except for diluted solutions in polycarbonate syringes, which should not be stored for more than 24 hours.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not freeze.
For storage conditions after first opening/dilution of the medicinal product, see section 6.3.
For further information on use after opening see section 6.6.

6.5 Nature and contents of container

1 ml (or 10 ml) clear glass ampoules (type I) in packs of 5 <Product name> 2 [10, 20, 50] mg/ml > ampoules.

6.6 Special precautions for disposal and other handling

Incompatibilities were observed with diluted solutions of 50 mg/ml when stored in polycarbonate syringes beyond 24 hours at 25°C. Whereas no evidence of incompatibility was found when the same preparations were stored at 4°C up to 7 days.

No evidence of incompatibility was observed between <Product name> undiluted and diluted with sodium chloride 9 mg/ml (0.9%) solution for infusion, glucose 50 mg/ml (5%) solution for infusion or water for injections, and representative brands of polypropylene syringes, polyethylene and PVC tubing and PVC or EVA infusion bags.

No evidence of incompatibility was observed between <Product name> undiluted and diluted with sodium chloride 9 mg/ml (0.9%) solution for infusion or water for injections and representative brands of injectable forms of the following medicinal products, when stored in high and low dose combinations in polypropylene syringes over a 24 hour period at ambient temperature (25°C):

Hyoscine butylbromide
Hyoscine hydrobromide
Dexamethasone sodium phosphate
Haloperidol
Midazolam hydrochloride
Metoclopramide hydrochloride
Levomepromazine hydrochloride
Glycopyrronium bromide
Ketamine hydrochloride

Inappropriate handling of the undiluted solution after opening of the original ampoule, or of the diluted solutions may compromise the sterility of the product.

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

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

20 December 2022