SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Hydromorphone Kalceks 20 mg/ml
solution for injection/infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml ampoule contains 20 mg hydromorphone hydrochloride (corresponding to 17.73 mg hydromorphone).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection/infusion.
Clear colourless or yellowish solution, free from visible particles.
pH of solution is 3.5-4.5.
Osmolality of solution is approximately 280 mOsm/kg.

4. CLINICAL PARTICULARS

WARNING: RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS
• Concomitant use of benzodiazepines with other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death (see section 4.4).
• Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.
• Limit dosages and durations to the minimum required.
• Follow patients for signs and symptoms of respiratory depression and sedation.

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 Hydromorphone Kalceks 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 a sufficiently high dose should generally be administered, the smallest dose to achieve analgesia should be aimed at in the individual case.

Before administering doses that require very small volumes, Hydromorphone Kalceks 20 mg/ml should be diluted.
The reservoir of a pain pump can be filled with individual dose of 20 mg as the dose control is secured by the pump calibration.

Hydromorphone 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	**Bolus**	**Infusion**
Adults and adolescents (> 12 years)		
subcutaneous (SC) use	1-2 mg SC every 3-4 hours	0.15-0.45 mg/h 0.004 mg/kg bodyweight/h
intravenous (IV) use	0.2-1 mg IV 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* (SC and IV)	0.2 mg bolus, stop interval 5-10 min.	
Children (< 12 years)	Not recommended	

*- patient controlled analgesia

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.

Switching from other opioids to hydromorphone:
Studies in which both intravenous and subcutaneous hydromorphone were given to healthy volunteers and patients show that hydromorphone (on a per milligram basis) was 5 to 10 times more potent than parenteral morphine. When switching from another opioid, treatment with hydromorphone should be initiated at a dose equivalent to approximately 1/10th of the corresponding parenteral morphine dose. This dose should be individually titrated to achieve optimal pain relief whilst considering patient safety.

Paediatric population
Hydromorphone Kalceks is not recommended for use in children under 12 years of age due to insufficient data on safety and efficacy.

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).

Method of administration
For intravenous injection or infusion and subcutaneous injection or infusion.
Hydromorphone Kalceks is intended for single use only.
The medicinal product is to be visually inspected prior to use. Only clear solutions free from particles should be used.
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 or infirm patients and in patients with severely impaired renal or hepatic function (see section 4.2). In all these patients, reduced dosage may be advisable.

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 Hydromorphone Kalceks 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 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 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 Kalceks may very rarely occur in particular in high doses. A hydromorphone dose reduction or change in opioid may be required.

Hydromorphone 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 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 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.

The use of hydromorphone may produce positive results in doping controls.

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

Concomitant use of Hydromorphone Kalceks 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 Kalceks 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).

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.

This medicinal product contains less than 1 mmol sodium (23 mg) per ml, that is to say essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

Central nervous system (CNS)
Centrally acting medicinal products such as tranquillisers, anaesthetics (e.g. barbiturates), hypnotics and sedatives, neuroleptics, antidepressants, antiemetics, antihistamines and other opioids or alcohol may enhance the CNS depressant effects of either drug.
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).
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
Opioids pass the placenta. 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. Hydromorphone should not be used in pregnancy unless clearly necessary.

Hydromorphone 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 Kalceks should not be used during breast-feeding.

Fertility
No data are available on the potential effects of hydromorphone on human fertility. No effects on male or female fertility were observed in animal studies (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

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

Metabolism and nutrition disorders:
Common: anorexia

Psychiatric disorders:
Common: anxiety, confusional state, insomnia, hallucinations
Uncommon: depression, dysphoria, euphoria, nightmares
Rare: drug dependence, agitation
Very rare: aggression

Nervous system disorders:
Very common: dizziness, somnolence
Uncommon: headache, tremor, myoclonus, paraesthesia
Rare: convulsions, sedation
Very rare: hyperalgesia (see section 4.4)
Not known: central sleep apnoea syndrome

Eye disorders:
Uncommon: miosis, blurred vision

Cardiac disorders:
Uncommon: tachycardia
Rare: bradycardia, palpitations

Vascular disorders:
Common: hypotension

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

Gastrointestinal disorders:
Very common: constipation, nausea, vomiting
Common: abdominal pain, dry mouth
Uncommon: dyspepsia, diarrhoea, dysgeusia
Very rare: paralytic ileus

Hepato-biliary disorders:

Uncommon:	hepatic enzymes increased
Rare:	biliary colic, elevation of pancreatic enzymes,

Skin and subcutaneous tissue disorders:

Very common:	pruritus
Common:	rash, sweating
Uncommon:	urticaria
Rare:	facial flushing

Renal and urinary disorders:

Common:	urinary retention, urgency

Reproduction system and breast disorders:

Uncommon:	decreased libido, erectile dysfunction

General disorders and administration site conditions:

Very common:	asthenic conditions
Common:	injection site reactions
Uncommon:	drug tolerance, drug withdrawal syndrome*, malaise and fatigue
Very rare:	peripheral oedema, injection site induration (particularly after repeated SC administration), injection site irritation
Not known:	hot flush, drug withdrawal syndrome neonatal

*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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il/

4.9 Overdose

Signs of hydromorphone intoxication and overdose include miosis, bradycardia, respiratory depression, hypotension, somnolence progressing to stupor and coma. Aspiration pneumonia may occur. 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 alkaloids,
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.

Opioids may influence the hypothalamic-pituitary-adrenal or -gonadal axes. The reported changes include an increase in serum prolactin and decreases in plasma cortisol and testosterone. Clinical symptoms resulting from these hormonal changes may become manifest.

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 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).

Distribution
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 IV 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).

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.

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

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity. Long-term carcinogenicity studies have not

been performed.
No effects on male or female fertility or sperm parameters were observed in rats at oral hydromorphone doses as high as 1.4 times the expected human dose on a 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 an active substance exposure almost four times above exposure in humans, but not in rats at an exposure about 1.8 times the human exposure.
Perinatum and postpartum rat pup (F1) mortality was increased and bodyweights were reduced during lactation period.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Citric acid
Sodium citrate
Sodium hydroxide (for pH adjustment)
Hydrochloric acid, concentrated (for pH adjustment)
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

Unopened ampoule: The expiry date of the product is indicated on the packaging materials.

Shelf life after first opening: The medicinal product should be used immediately after opening the ampoule.

Shelf life after dilution:
Chemical and physical in-use stability has been demonstrated for 7 days at 25°C and 2-8°C (see section 6.6).
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 store above 25°C. Keep the ampoules in the outer carton in order to protect from light. Do not freeze.

For storage conditions after dilution or first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of containers

Type I amber glass ampoules of 1 ml.

Pack size:
5 or 10 ampoules of 1 ml
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Hydromorphone Kalceks undiluted or diluted with sodium chloride 9 mg/ml solution for infusion, glucose 50 mg/ml solution for infusion or water for injections, is physically and chemically stable when in contact with representative brands of polypropylene syringes, polyethylene or PVC tubing, and PVC or EVA infusion bags.

As well as product is compatible with following medicinal products: hyoscine butylbromide, hyoscine hydrobromide, dexamethasone sodium phosphate, haloperidol, midazolam hydrochloride, metoclopramide hydrochloride, levomepromazine hydrochloride, glycopyrronium bromide, ketamine hydrochloride.

The medicinal product is to be visually inspected prior to use. Only clear solutions free from particles should be used. For single use only.

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

A.L.Medi-Market Ltd., 3 Hakatif street, Emek Hefer Industrial Park, 3877701

8. MARKETING AUTHORISATION NUMBER(S)

174-70-36834-99

9. MANUFACTURER

AS Kalceks, Krustpils iela 71E, Rīga, LV-1057, Latvia

10. DATE OF REVISION OF THE TEXT

Approved in April 2025