Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Loperamide Grindeks 2 mg hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 2 mg loperamide hydrochloride.

Excipient with known effect: each capsule contains 95 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard capsule.
Hard gelatin capsules No. 3 (approximately 16 mm × 6 mm) with pink body and dark-green cap, the content - white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the symptomatic treatment of acute diarrhoea in adults and adolescents over 12 years of age.

4.2 Posology and method of administration

Posology

Adults
The initial dose is 2 capsules (4 mg) followed by 1 capsule (2 mg) after each subsequent loose stool. The total daily dose should not exceed 6 capsules (12 mg).

Adolescents over 12 years of age
The initial dose is 2 capsules (4 mg) followed by 1 capsule (2 mg) after each subsequent loose stool. The total daily dose should not exceed 4 capsules (8 mg).

Children below 12 years of age
Limited data are available for the use in children below 12 years of age (see Section 4.8).
For children aged 2-12 years other loperamide medicinal products with a different pharmaceutical form (e.g., oral solution) and a lower strength may be more appropriate. Use in children aged 2-12 years cannot be made without medical prescription. Children below 2 years of age, see section 4.3.

The maximum duration of treatment is 48 hours.

Elderly
No dose adjustment is required for the elderly.

Renal impairment
No dose adjustment is required for patients with renal impairment.

Hepatic impairment
Although no pharmacokinetic data are available in patients with hepatic impairment, loperamide hydrochloride should be used with caution in such patients because of reduced first pass metabolism (see section 4.4).

Method of administration

For oral use.
Loperamide Grindeks capsules should be swallowed in a whole, with some liquid. The capsules should not be chewed because of bitter taste. The capsules can be taken any time during the day with or without food.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Loperamide hydrochloride must not be used in children below 2 years of age.
- Loperamide hydrochloride must not be used as the primary therapy:
- in patients with acute dysentery accompanied by high fever and blood in the stools
- in patients with acute ulcerative colitis
- in patients with pseudomembranous colitis associated with the use of broad spectrum antibiotics
- in patients with bacterial enterocolitis caused by invasive organisms like *Salmonella, Shigella,* and *Campylobacter*.

Loperamide hydrochloride must not be used in conditions when the inhibition of peristalsis can be harmful (e.g. ileus, subileus, megacolon, toxic megacolon etc). Loperamide hydrochloride must be discontinued promptly if constipation, abdominal distension or ileus develop.

4.4 Special warnings and precautions for use

Patients should be advised to consult a doctor immediately in case of formed and unusually hard stool or in case if patient stops feeling bowel movements while on treatment with this medicinal product.

The treatment does not replace antibacterial treatment in infectious diarrhoea.

Patients should be advised to discontinue treatment and to consult their doctor in acute diarrhoea if clinical improvement is not observed within 48 hours.

Treatment of diarrhoea with loperamide hydrochloride is only symptomatic. Whenever an underlying etiology can be determined, specific treatment should be given when appropriate. The priority in acute diarrhoea is the prevention or reversal of fluid and electrolyte depletion. In case of dehydration, administration of suitable fluid and electrolyte replacement therapy is then the most important measure. This is particularly important in young children and in frail and elderly patients with acute diarrhoea. In case of dehydration, a patient may become dizzy and start vomiting. A dry mouth can also be a sign of dehydration.

Patients with AIDS treated with this medicine for diarrhoea should have therapy stopped at the earliest signs of abdominal bloating. There have been reports of toxic megacolon in AIDS patients with infectious colitis from both viral and bacterial pathogens treated with loperamide hydrochloride.

Although no pharmacokinetic data are available in patients with hepatic impairment, loperamide hydrochloride should be used with caution in such patients because of reduced first pass metabolism.
This medicine should be used with increased precaution by patients with hepatic impairment as relative overdose may lead to CNS toxicity.

Cardiac events including QT interval and QRS complex prolongation and *torsades de pointes* have been reported in association with overdose. Some cases had a fatal outcome (see section 4.9). Overdose can unmask existing Brugada syndrome. Patients should not exceed the recommended dose and/or the recommended duration of treatment.

Excipients
Patients should be advised that each Loperamide Grindeks capsule contain 95 mg 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 interaction

Non-clinical data have shown that loperamide is a P-glycoprotein substrate. Concomitant administration of loperamide (16 mg single dose) with quinidine or ritonavir (P-glycoprotein inhibitors) showed 2 to 3-fold increase in loperamide plasma levels. The

clinical relevance of this pharmacokinetic interaction with P-glycoprotein inhibitors, when loperamide is given at recommended dosages (2 to 16 mg daily), is unknown.

The concomitant administration of loperamide (4 mg single dose) and itraconazole, an inhibitor of CYP3A4 and P-glycoprotein, resulted in a 3 to 4-fold increase in loperamide plasma concentrations. In the same study a CYP2C8 inhibitor, gemfibrozil, increased loperamide by approximately 2-fold. The combination of itraconazole and gemfibrozil resulted in a 4-fold increase in peak plasma levels of loperamide and a 13-fold increase in total plasma exposure. These increases were not associated with central nervous system effects as measured by psychomotor tests (such as subjective drowsiness and the Digit Symbol Substitution Test).

The concomitant administration of loperamide (16 mg single dose) and ketoconazole, an inhibitor of CYP3A4 and P-glycoprotein, resulted in a 5-fold increase in loperamide plasma concentrations. This increase was not associated with increased pharmacodynamic effects as measured by pupillometry.

Concomitant treatment with oral desmopressin resulted in a 3-fold increase of desmopressin plasma concentrations, presumably due to slower gastrointestinal motility.

It is expected that drugs with similar pharmacological properties may potentiate the effect of loperamide hydrochloride and that drugs that accelerate gastrointestinal transit may decrease its effect.

Loperamide may interact with saquinavir, St. John's wort and valerian.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is a limited amount of data from the use of loperamide hydrochloride in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of loperamide hydrochloride during pregnancy, especially in the first trimester.

Breast-feeding
Small amounts of loperamide may be excreted in human breast milk. Therefore, this medicine is not recommended to use during breast-feeding.
Women who are pregnant or breastfeeding should consult their doctor on the use of this medicine.

Fertility
There are no data available on effects of loperamide hydrochloride on fertility in humans. Results of animal studies do not indicate any effect of loperamide hydrochloride on fertility at therapeutic doses.

4.7 Effects on ability to drive and use machines

Loperamide Grindeks has moderate influence on the ability to drive and use machines. Tiredness, dizziness or drowsiness may occur when diarrhoea is treated with loperamide hydrochloride, therefore, it is advisable to use caution when driving or performing potentially hazardous work.

4.8 Undesirable effects

Adults and adolescents aged ≥ 12 years
The safety of loperamide hydrochloride was evaluated in a total 3076 adults and adolescents aged ≥ 12 years who participated in 31 controlled and uncontrolled clinical trials in the treatment of diarrhoea.
Of these, 2755 patients were treated for acute diarrhoea in 26 studies and 321 patients with chronic diarrhoea were treated in 5 studies.

The most commonly reported (≥ 1% incidence) adverse drug reactions in clinical trials with loperamide hydrochloride in acute diarrhoea were: constipation (2.7%), flatulence (1.7%), headache (1.2%) and nausea (1.1%). The most commonly reported (≥ 1% incidence) adverse drug reactions in clinical trials with patients with chronic diarrhoea were: flatulence (2.8%), constipation (2.2%), nausea (1.2%) and dizziness (1.2%).

The frequency categories use the following convention: 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); and very rare (<1/10,000), not known (cannot be estimated from the available data).

Table 1 ADRs reported with the use of loperamide hydrochloride from the clinical trials with adults and adolescents aged ≥ 12 years or post-marketing experience

System organ class	Indication	
	Acute diarrhoea (N=2755)	**Post-marketing experience**
Immune system disorders		
Hypersensitivity reaction*		Rare
Anaphylactic reaction (including anaphylactic shock)*		Rare
Anaphylactoid reaction*		Rare
Nervous system disorders		
Headache	Common	
Dizziness	Uncommon	
Somnolence*		Uncommon
Loss of consciousness*		Rare
Stupor*		Rare
Depressed level of consciousness*		Rare
Hypertonia*		Rare
Coordination difficulty*		Rare
Eye disorders		
Miosis*		Rare
Gastrointestinal disorders		
Acute pancreatitis		Not known
Constipation, nausea, flatulence	Common	
Abdominal pain, abdominal discomfort, dry mouth	Uncommon	
Abdominal pain upper, vomiting	Uncommon	
Abdominal distension	Rare	
Ileus* (including paralytic ileus)		Rare
Megacolon* (including toxic megacolon)		Rare
Glossalgia*		Rare
Skin and subcutaneous tissue disorders		
Rash	Uncommon	
Bullous eruption* (including Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme)		Rare
Angioedema*		Rare
Urticaria*		Rare
Pruritus*		Rare
Renal and urinary disorders		
Urinary retention*		Rare
General disorders and administration site conditions		
Fatigue*		Rare

* Symptoms reported in the post-marketing setting. Since post-marketing reports did not differentiate between chronic and acute indications or adult or children population, the frequency is estimated from all clinical trials with loperamide hydrochloride.

Paediatric population

The safety of loperamide hydrochloride was evaluated in 607 children aged 10 days to 13 years who participated in a total 13 controlled and uncontrolled clinical trials in the treatment of acute diarrhoea. In general, adverse reactions in this population were comparable with those seen in clinical trials conducted with adults and adolescents aged 12 years and over.

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 HPRA Pharmacovigilance Website: www.hpra.ie.

4.9 Overdose

Symptoms
In case of overdose (including relative overdose due to hepatic dysfunction) CNS depression (stupor, coordination abnormality, somnolence, miosis, muscular hypertonia and respiratory depression), dry mouth, abdominal discomfort, nausea, vomiting, constipation, urinary retention and ileus may occur.

Children may be more sensitive to CNS effects compared to adults.

In individuals who have ingested overdoses of loperamide (40 mg to 792 mg doses were reported), cardiac events such as QT interval and QRS complex prolongation and/or other serious ventricular arrhythmias (including *torsades de pointes),* cardiac arrest and syncope have been observed (see section 4.4). Fatal cases have also been reported. Overdose can unmask existing Brugada syndrome.

Treatment

In cases of overdose, ECG monitoring for QT interval prolongation should be initiated.

If CNS symptoms of overdose occur, naloxone can be given as an antidote. Since the duration of action of loperamide is longer than that of naloxone (1 to 3 hours), repeated treatment with naloxone might be indicated. Therefore, the patient should be monitored closely for at least 48 hours in order to detect possible CNS depression.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Antipropulsives; ATC code: A07DA03

Mechanism of action
Loperamide binds to the opiate receptor in the gut wall, reducing propulsive peristalsis, increasing intestinal transit time by inhibiting the release of acetylcholine and prostaglandin. Loperamide increases the absorption of water and electrolytes, especially in the ileum. Loperamide also increases the tone of the anal sphincter, which helps reduce faecal incontinence and urgency.
Due to its high affinity to the intestinal wall and high first pass metabolism, loperamide hardly enters the systemic circulation.

5.2 Pharmacokinetic properties

Absorption
Most ingested loperamide is absorbed from the gut, but as a result of its significant first pass metabolism, systemic bioavailability is only approximately 0.3%.

Distribution
Studies on distribution in rats show a high affinity for the gut wall with a preference for binding to receptors of the longitudinal muscle layer. The plasma protein binding of loperamide is 95%, mainly to albumin. Non-clinical data have shown that loperamide is a P-glycoprotein substrate.

Biotransformation
Loperamide is almost completely extracted by the liver, where it is predominantly metabolised, conjugated and excreted via the bile. Oxidative N-demethylation is the main metabolic pathway for loperamide and is mediated mainly through CYP3A4 and CYP2C8. Due to this very high first pass effect, plasma concentrations of unchanged drug remain extremely low.

Elimination

The half-life of loperamide in man is about 11 hours with a range of 9 to 14 hours. Excretion of the unchanged loperamide and the metabolites mainly occurs through the faeces.

Paediatric population
No pharmacokinetic studies were performed in the paediatric population. It is expected that the pharmacokinetic behaviour of loperamide and the interactions of other drugs with loperamide will be comparable to those in adults.

5.3 Preclinical safety data

Pre-clinical effects were only observed at exposures that exceed the maximum human exposure significantly suggesting minor clinical relevance. In acute and chronic studies performed with loperamide no relevant toxicity was observed.

Non-clinical in vitro and in vivo evaluation of loperamide indicates no significant cardiac electrophysiological effects within its therapeutically relevant concentration range and at significant multiples of this range (up to 47-fold). However, at extremely high concentrations associated with deliberate overdosing (see section 4.4), loperamide has cardiac electrophysiological actions consisting of inhibition of potassium (hERG) and sodium currents, and arrhythmias.

No indications of mutagenic effects were found in vivo and in vitro studies on loperamide hydrochloride and loperamide hydrochloride oxide, a prodrug of loperamide hydrochloride. Carcinogenicity studies with loperamide hydrochloride showed no indications of tumourigenic potential.

Loperamide had no effect on fertility in male rats when administered orally prior to mating at doses up to approximately 40 mg/kg. In studies on reproductive toxicity no relevant effects were observed on fertility, embryofetal development and lactation after administration of maternal nontoxic doses. No indications of teratogenicity were observed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Magnesium stearate (E572)

Capsule shells: Gelatin (E441)
Titanium dioxide (E171)
Iron oxide red (E172)
Iron oxide yellow (E172)
Brilliant blue FCF (E133)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This product does not require any special storage conditions.

6.5 Nature and contents of container

Pack sizes: 6, 8, 10, 12, 16, 18 or 20 capsules in PVC/Alu blisters are packed in a cardboard box.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7 MARKETING AUTHORISATION HOLDER

AS Grindeks
Krustpils Iela 53
Riga
1057
Latvia

8 MARKETING AUTHORISATION NUMBER

PA22992/027/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 4th April 2025

10 DATE OF REVISION OF THE TEXT

February 2026