Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Loperamide hydrochloride 2 mg Oral Lyophilisate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Loperamide hydrochloride 2 mg equivalent to loperamide 1.85 mg per oral lyophilisate

Excipients with known effect: 1.0 mg aspartame (E951)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

oral lyophilisate.

White to off-white, round, tablets, debossed with T on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic treatment of acute diarrhoea in adults and adolescents aged 12 years and over.

4.2 Posology and method of administration

Posology

Adults
Two oral lyophilisates (4 mg) initially followed by 1 oral lyophilisate (2 mg) after every loose stool, not earlier than 1 hour after the initial dose. The usual dose is 3-4 oral lyophilisates (6 mg-8 mg) daily; the maximum daily dose should not exceed 6 oral lyophilisates (12 mg).

Adolescents aged 12 years and older
One oral lyophilisate (2 mg) initially followed by 1 oral lyophilisate (2 mg) after every loose stool, not earlier than 1 hour after the initial dose.
The maximum daily dose should not exceed 4 oral lyophilisates (8 mg).

The maximum duration of treatment without consultation with a doctor is 2 days.

Children
This medicinal product is not intended for children between 2 and 12 years of age.

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, this medicine should be used with caution in such patients because of reduced first pass metabolism (see section 4.4).

Method of administration:

The oral lyophilisate should be placed on your tongue, where it dissolves and can be swallowed with the saliva. No liquid intake is needed for the oral lyophilisate.

4.3 Contraindications

Loperamide hydrochloride is contraindicated in:

- patients with a known hypersensitivity to loperamide hydrochloride or to any of the excipients listed in section 6.1.
- children aged less than 2 years of age
- patients with acute dysentery, which is characterised by blood in stools and elevated body temperature.
- patients with acute ulcerative colitis
- patients with bacterial enterocolitis caused by invasive organisms including Salmonella, Shigella and Campylobacter
- patients with pseudomembranous colitis associated with the use of broad spectrum antibiotics

Loperamide hydrochloride should not be used when inhibition of peristalsis is to be avoided due to the possible risk of significant sequelae including ileus, megacolon and toxic megacolon.

Loperamide hydrochloride should be discontinued promptly when ileus or constipation are present or when abdominal distension develops.

4.4 Special warnings and precautions for use

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. This is particularly important in young children and in frail and elderly patients with acute diarrhoea. Use of loperamide hydrochloride does not preclude the administration of appropriate fluid and electrolyte replacement therapy.

Since persistent diarrhoea can be an indicator of potentially more serious conditions, loperamide hydrochloride should not be used for prolonged periods until the underlying cause of the diarrhoea has been investigated.

In acute diarrhoea, if clinical improvement is not observed within 48 hours, the administration of loperamide hydrochloride should be discontinued and patients should be advised to consult their doctor.

Loperamide hydrochloride should be stopped as soon as bowel movements solidify or as soon as there are no further bowel movements for more than 12 hours.

Patients with AIDS treated with loperamide hydrochloride for diarrhoea should discontinue treatment at the earliest signs of abdominal distension. There have been isolated reports of obstipation with an increased risk for 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, as it may result in a relative overdose leading to central nervous system (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.

This medicine contains less than 1 mmol (23 mg) sodium per oral lyophilisate, that is to say essentially 'sodium-free'.

This medicine contains 1.0 mg aspartame in each oral lyophilisate. Aspartame is a source of phenylalanine. It may be harmful if you have phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.

4.5 Interaction with other medicinal products and other forms of interaction

Non-clinical data have shown that loperamide hydrochloride is a P-glycoprotein substrate. Concomitant administration of loperamide hydrochloride (16 mg single dose) with quinidine, or ritonavir, which are both P-glycoprotein inhibitors, resulted in a 2 to 3-fold increase in loperamide hydrochloride plasma levels. The clinical relevance of this pharmacokinetic interaction with P-glycoprotein inhibitors, when loperamide hydrochloride is given at recommended dosages is unknown.

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

The concomitant administration of loperamide hydrochloride (16 mg single dose) and ketoconazole, an inhibitor of CYP3A4 and P-glycoprotein, resulted in a 5-fold increase in loperamide hydrochloride 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 loperamide's effect and that drugs that accelerate gastrointestinal transit may decrease its effect.

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.

Breast-feeding
No effects on the breastfed newborn/infant are anticipated since the systemic exposure of the breast-feeding woman to loperamide is negligible. Loperamide may be prescribed temporarily during breastfeeding if dietary measures are insufficient

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

Tiredness, dizziness or drowsiness may occur in the setting of diarrhoeal syndromes treated with loperamide. Therefore, it is advisable to use caution when driving a car or operating machinery.

4.8 Undesirable effects

Paediatric population

The safety of loperamide hydrochloride was evaluated in 607 patients aged 10 days to 13 years of age who participated in 13 controlled or uncontrolled clinical studies using loperamide hydrochloride in the treatment of acute diarrhoea. Overall, the adverse reaction profile in this patient population was similar to that observed in clinical studies with loperamide hydrochloride in adults and adolescents over 12 years of age.

Adults and children aged ≥ 12 years

The safety of loperamide hydrochloride was evaluated in 2755 adults and children aged ≥ 12 years who participated in 26 controlled and uncontrolled clinical trials of loperamide hydrochloride used for the treatment of acute diarrhoea.

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

Table 1 displays ADRs that have been reported with the use of loperamide hydrochloride from either clinical trial (acute diarrhoea) or post-marketing experience.

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).

Table 1: Adverse Drug Reactions

System Organ Class	Common	Uncommon	Rare
Immune System Disorders			Hypersensitivity reaction[a] Anaphylactic reaction (including Anaphylactic shock)[a] Anaphylactoid reaction[a]
Nervous System Disorders	Headache	Dizziness Somnolence[a]	Loss of consciousness[a] Stupor[a] impaired level of consciousness[a] Muscular Hypertonia[a] Coordination abnormality[a]
Eye Disorders			Miosis[a]
Gastrointestinal Disorders	Constipation Nausea Flatulence	Abdominal pain Abdominal discomfort Dry mouth Pain in upper abdomen Vomiting Dyspepsia[a]	Ileus[a] (including paralytic ileus) Megacolon[a] (including toxic megacolon[b]) Abdominal distension Glossodynia[c]
Skin and Subcutaneous Tissue Disorders		Rash	Bullous eruption[a] (including Stevens-Johnson syndrome, Toxic epidermal necrolysis and Erythema multiforme) Angioedema[a] Urticaria[a] Pruritus[a]
Renal and Urinary Disorders			Urinary retention[a]
General Disorders and Administration Site Conditions			Fatigue[a]

a: Inclusion of this term is based on post-marketing reports for loperamide hydrochloride. As the process for determining post marketing ADRs did not differentiate between chronic and acute indications or adults and children the frequency is estimated from all clinical trials with loperamide hydrochloride (acute and chronic), including trials in children ≤12 years (N=3683).
b: See section 4.4 Special Warnings and Special Precautions for use.
c: Only reported for the orodispersible tablet.

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:
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), constipation, urinary retention and ileus may occur. Children, and patients with hepatic dysfunction, may be more sensitive to CNS effects.

In individuals who have ingested overdoses of loperamide hydrochloride, cardiac events such as QT interval and QRS complex prolongation, torsades de pointes, other serious ventricular arrhythmias, 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 hydrochloride 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 any possible depression of the central nervous system.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Antidiarrhoeals, intestinal antiinflammatory/antiinfective agents, antipropulsives

ATC code: A07DA03

Loperamide hydrochloride binds to the opiate receptor in the gut wall, reducing propulsive peristalsis, increasing intestinal transit time and enhancing resorption of water and electrolytes. Loperamide hydrochloride increases the tone of the anal sphincter, which helps reduce faecal incontinence and urgency.

In a double blind randomised clinical trial in 56 patients with acute diarrhoea receiving loperamide, onset of antidiarrhoeal action was observed within one hour following a single 4 mg dose. Clinical comparisons with other antidiarrhoeal drugs confirmed this exceptionally rapid onset of action of loperamide.

5.2 Pharmacokinetic properties

Absorption: Most ingested loperamide hydrochloride is absorbed from the gut, but as a result of 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 hydrochloride is 95%, mainly to albumin. Nonclinical data have shown that loperamide hydrochloride is a P-glycoprotein substrate.

Metabolism: Loperamide hydrochloride is almost completely extracted by the liver, where it is predominantly metabolized, conjugated and excreted via the bile. Oxidative N-demethylation is the main metabolic pathway for loperamide hydrochloride, 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 hydrochloride in man is about 11 hours with a range of 9-14 hours. Excretion of the unchanged loperamide hydrochloride and the metabolites mainly occurs through the faeces.

5.3 Preclinical safety data

Pre-clinical effects were only observed at exposures that exceed the maximum human exposure significantly suggesting minor clinical relevance.

Non-clinical in vitro and in vivo evaluation of loperamide hydrochloride 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 overdoses (see section 4.4), loperamide hydrochloride 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.

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

Pullulan (E1204)
Mannitol (E421)
Sodium hydrogen carbonate (E500),
Aspartame (E951)
Polysorbate 80 (E433),
Peppermint flavour (corn maltodextrin, flavouring Ingredients and modified waxy maize starch, 1450).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blister packaging in packs of 6 or 12 and 10 oral lyophilisates.

The blister comprising PVC/polyamide/aluminium/PVC blister with peel-off lidding of paper/PET/aluminium foil.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

To remove the oral lyophilisate from the blister:

- lift the edge of the foil;
- peel off the foil completely;
- tip the oral lyophilisate out;
- remove the oral lyophilisate from the blister.

Do not push oral lyophilisate through foil.

7 MARKETING AUTHORISATION HOLDER

Tenshi Kaizen B.V.
Kingsfordweg 151
1043 GR Amsterdam
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA22851/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11th March 2022

10 DATE OF REVISION OF THE TEXT

July 2022