SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Loperamid Brown 2 mg capsules, hard

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 2mg Loperamide Hydrochloride.
Excipient with known effect:
Each tablet contains 132.00 mg lactose monohydrate, 0.0013 mg carmoisine, and 0.0009 Sunset yellow FCF.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule, hard.
Green opaque cap, grey opaque body, size '4', hard gelatin capsules, filled with white to off white powder. Approximately 14 mm in length.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the symptomatic treatment of acute diarrhoea of any aetiology including acute exacerbations of chronic diarrhoea for periods of up to 5 days in adults and children aged 12 years and over. For the symptomatic treatment of chronic diarrhoea in adults.

4.2 Posology and method of administration

Posology

ACUTE DIARRHOEA

Adults and children over 12:
Two capsules initially, followed by one capsule after each loose stool. The usual dose is 3-4 capsules a day. The total daily dose should not exceed 8 capsules.

CHRONIC DIARRHOEA
Studies have shown that patients may need widely differing amounts of Loperamide. The starting dose should be between two and four capsules per day in divided doses, depending on severity. If required, this dose can be adjusted according to result up to a maximum of eight capsules daily.
Having established the patient's daily maintenance dose, the capsules may be administered on a twice daily regimen. Tolerance has not been observed and therefore subsequent dosage adjustment should be unnecessary.

Paediatric population
<Product Name> is contraindicated in children less than 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, <Product Name> should be used with caution in such patients because of reduced first pass metabolism. (see 4.4 Special warnings and special precautions for use).

Method of administration

Oral use. The capsules should be taken with liquid.

4.3 Contraindications

This medicine is contraindicated:
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

- in children less than 12 years of age.
- in patients with acute dysentery, which is characterised by blood in stools and high fever.
- in patients with acute ulcerative colitis.
- in patients with bacterial enterocolitis caused by invasive organisms including Salmonella,Shigella and Campylobacter.
- in patients with pseudomembranous colitis associated with the use of broad spectrum antibiotics.

<Product Name> must 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. <Product Name> must be discontinued promptly when ileus, constipation or abdominal distension develops.

4.4 Special warnings and precautions for use

In chronic inflammatory bowel diseases, as loperamide can mask the symptoms in case of acute deterioration. Treatment with <Product Name> is only symptomatic, therefore causal therapy should be given first.

Dehydration and electrolyte disturbances may occur in patients with diarrhoea, especially in children. It is important to pay attention to appropriate fluid and electrolyte substitution.

Treatment with <Product Name> must be discontinued if there are signs of constipation or other signs of insufficient peristalsis.

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

Patients with AIDS treated with this medicine for diarrhoea should have therapy stopped 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, this medicine should be used with caution in such patients because of reduced first pass metabolism, as it may result in a relative overdose leading to CNS toxicity.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine because it contains lactose

Cardiac events including QT interval and QRS complex prolongation and torsade 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.

Combination with high-dose loperamide and drugs that inhibit P-glycoprotein (quinidine, ritonavir, cyclosporine, verapamil and certain macrolide antibiotics, e.g. erythromycin and clarithromycin) should be done with caution (see section 4.5).

There are limited data available regarding the treatment of children under 12 years of age. See section 4.8.

4.5 Interaction with other medicinal products and other forms of interaction

Cholestyramine possibly reduces the absorption of loperamide. The agents should not be taken at the same time but at intervals of a couple of hours.

Non-clinical data have shown that loperamide is a P-glycoprotein which i.a. is found in the blood-brain barrier substrate. Concomitant administration of loperamide (16 mg single dose) with quinidine, or ritonavir, which are both P-glycoprotein inhibitors, resulted in a 2 to 3-fold increase in loperamide plasma levels. Theoretically, increased distribution to the CNS can also be obtained. The clinical relevance of this pharmacokinetic interaction with P-glycoprotein inhibitors, when loperamide is given at recommended dosages, is unknown, but the risk of central decreased sensitivity to carbon dioxide and thus an effect on respiration cannot be excluded (see section 4.4).

Combination with high-dose loperamide and drugs that inhibit P-glycoprotein, e.g. quinidine, ritonavir, ciclosporin, verapamil and certain macrolide antibiotics, e.g. erythromycin and clarithromycin, should be done with caution. Dose adjustment should be considered (see section 4.4).

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 the plasma concentration of 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 (CNS) effects as measured by psychomotor tests (i.e., 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 loperamide’s effect and that drugs that accelerate gastrointestinal transit may decrease its effect.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in human pregnancy has not been established, although from animal studies there are no indications that loperamide HCl possesses any teratogenic or embryotoxic properties. As with other drugs, it is not advisable to administer this medicine in pregnancy, especially during the first trimester.

Breast-feeding

Small amounts of loperamide may appear in human breast milk. Therefore, this medicine is not recommended during breast-feeding.

Women who are pregnant or breast feeding infants should therefore be advised to consult their doctor for appropriate treatment.

Fertility

The effect on human fertility has not been evaluated.

4.7 Effects on ability to drive and use machines

Loss of consciousness, depressed level of consciousness, tiredness, fatigue, dizziness, or drowsiness may occur when diarrhoea is treated with this medicine. Therefore, it is advisable to use caution when driving a car or operating machinery. See Section 4.8, Undesirable Effects.

4.8 Undesirable effects

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

The most commonly reported (i.e. ≧ 1% incidence) adverse drug reactions (ADRs) in clinical trials with loperamide HCl in acute diarrhoea were: constipation (2.7%), flatulence (1.7%), headache (1.2%) and nausea (1.1%). In chronic diarrhea clinical trials, the most commonly reported (i.e. ≥ 1% incidence) adverse reactions were: flatulence (2.8%), constipation (2.2%), nausea (1.2%) and dizziness (1.2%).

Table 1 displays ADRs that have been reported with the use of loperamide HCl 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); very rare (<1/10,000); not known (cannot be estimated from the available data).

Table 1: Adverse Drug Reactions

	Indication			
System Organ Class	**Common**	**Uncommon**	**Rare**	**Not known**
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] Depressed level of	

			consciousness[a] Hypertonia[a] Coordination abnormality[a]	
Eye Disorders			Miosis[a]	
Gastrointestinal Disorders	Constipation Nausea Flatulence	Abdominal pain Abdominal discomfort Dry mouth Abdominal pain upper Vomiting Dyspepsia[a]	Ileusa (including paralytic ileus) Megacolona (including toxic megacolonb) Abdominal distension	Acute pancreatitis
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 HCl. 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 HCl (acute and chronic), including trials in children ≤ 12 years (N=3683).

b: See section 4.4 Special Warnings and Special Precautions for use.

Pediatric population

The safety of loperamide hydrochloride was evaluated in 607 patients aged 10 days to 13 years who participated in 13 controlled and uncontrolled clinical trials of loperamide hydrochloride used for treatment of acute diarrhea. In general, the adverse event profile of this patient population was similar to that of was seen in clinical trials of loperamide hydrochloride in adults and children ≥ 12 years of age.

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 [to be completed nationally].

4.9 Overdose

Toxicity:

1-2 mg/day to children of 1-6 months gave severe-very serious intoxication. 10 mg to 4-month old children produced very serious intoxication. 3 mg distributed over 16 hours to a 4-year-old gave

moderate, while 1 mg to a 1 1/2-year-old and a maximum of 12 mg to a 2-year-old (whose stomach was emptied) gave mild intoxication. 26 mg for adults did not cause any symptoms after gastric emptying.

Symptoms:
The symptoms are often delayed and in children can appear after repeated therapeutic dosing. In case of overdose (including relative overdose due to hepatic dysfunction), CNS depression (stupor, coordination abnormality, somnolence, miosis, muscular hypertonia and respiratory depression), apathy, dizziness, confusion, hallucinations, decreased consciousness, coma, apnea, increased or decreased muscle tone, opisthotonus, bradycardia, VES, hyperglycemia, nausea, vomiting, 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 HCl, cardiac events such as QT interval and QRS complex prolongation, torsade 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.

After cessation of use, cases of withdrawal syndrome have been observed in individuals who abuse, misuse or intentionally overdose with excessively large doses of loperamide.

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

Loperamide binds to the opiate receptor in the intestinal wall and inhibits the release of acetylcholine and prostaglandins, thereby reducing propulsive peristalsis, increasing intestinal transit time and enhancing resorption of water and electrolytes. Loperamide 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 anti-diarrhoeal 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

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

<u>Distribution</u>
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 metabolized, 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 9-14 hours. Excretion of the unchanged loperamide and the metabolites mainly occurs through the faeces.

5.3 Preclinical safety data

Acute and chronic studies on loperamide showed no specific toxicity. Results of *in vivo* and *in vitro* studies carried out indicated that loperamide is not genotoxic. In reproduction studies, very high doses (40 mg/kg/day – 20 times the maximum human use level (MHUL)), based on body surface area dose comparison (mg/m^2) loperamide impaired fertility and foetal survival in association with maternal toxicity in rats. Lower doses (≥ 10mg/kg/day – 5 times MHUL) revealed no effects on maternal or fetal health and did not affect peri- and post-natal development.

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 overdoses (see section 4.4), loperamide has cardiac electrophysiological actions consisting of inhibition of potassium (hERG) and sodium currents, and arrhythmias.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose Monohydrate
Pregelatinized Maize starch
Talc
Magnesium stearate

Capsule Shells:
Carmoisine (E 122)
Patent Blue V (E 131)
Quinoline Yellow (E 104)
Sunset Yellow FCF (E 110)
Titanium dioxide (E 171)
Gelatin
Iron Oxide Black (E 172)
Iron Oxide Red (E 172)
Iron Oxide Yellow (E 172)

6.2 Incompatibilities

None applicable

6.3 Shelf life

3 years for blister pack. (PVC/Aclar-aluminium)
2 years for blister pack. (Clear PVC-aluminium)
3 years for HDPE bottle.

After first opening of the HDPE bottle: 30 days

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

PVC/Aclar or Clear PVC -Aluminium blister packs containing 6, 10, 12, 18, 30, 40, 60 and 100's capsules & HDPE bottle pack of 250 capsules.

Not all pack sizes may be marketed

6.6 Special precautions for disposal

No special 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

Date of first authorisation: {DD month YYYY}

10. DATE OF REVISION OF THE TEXT

2024-12-19