SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Loperamide hydrochloride 2 mg Orodispersible Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each orodispersible tablet contains 2 mg loperamide hydrochloride.

Excipients with known effect:

Each Orodispersible tablet contains saccharose and also contains 5 mg of aspartame.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Orodispersible tablet

Round white to off white tablets with a diameter of approximately 7 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the symptomatic treatment of acute diarrhoea in adults and children aged 12 years and over.

For the symptomatic treatment of acute episodes of diarrhoea associated with Irritable Bowel Syndrome in adults aged 18 years and over following initial diagnosis by a doctor.

4.2 Posology and method of administration

Posology

ACUTE DIARRHOEA

Adults and children over 12:

Two orodispersible tablets (4 mg) initially, followed by one orodispersible tablet (2 mg) after each loose stool. The usual dose is 3-4 orodispersible tablets (6 mg – 8 mg) a day. The total daily dose should not exceed 6 orodispersible tablets (12 mg).

SYMPTOMATIC TREATMENT OF ACUTE EPISODES OF DIARRHOEA ASSOCIATED WITH IRRITABLE BOWEL SYNDROME IN ADULTS AGED 18 YEARS AND OVER

Two orodispersible tablets (4 mg) to be taken initially, followed by 1 orodispersible tablet (2 mg) after every loose stool, or as previously advised by your doctor. The maximum daily dose should not exceed 6 orodispersible tablets (12 mg).

Paediatric population

Loperamide hydrochloride is contraindicated in children less than 12 years of age.

Special populations

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 Special warnings and special precautions for use).

Method of administration

For oral use.

The orodispersible tablet is placed on the tongue. The tablet disintegrates immediately on the tongue and is swallowed with the saliva. No further fluid intake is required.

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.

Loperamide hydrochloride 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. Loperamide hydrochloride must be discontinued promptly when ileus, constipation or abdominal distension develop.

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 this medicine does not preclude the administration of appropriate fluid and electrolyte replacement therapy.

Since persistent diarrhoea can be an indicator of potentially more serious conditions, this medicine 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.

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, 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 CNS toxicity.

If patients are taking this medicine to control episodes of diarrhoea associated with Irritable Bowel Syndrome previously diagnosed by their doctor, and clinical improvement is not observed within 48 hours, the administration of Loperamide HCl should be discontinued and they should consult with their doctor. Patients should also return to their doctor if the pattern of their symptoms changes or if the repeated episodes of diarrhoea continue for more than two weeks.

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.

In individuals with opioid dependence, abuse and misuse of loperamide for opioid substitution have been reported (see section 4.9).

Caution is needed in patients with a history of drug abuse. Loperamide is an opioid with low bioavailability and limited potential to penetrate the blood brain barrier at therapeutic doses. However, addiction is observed with opioids as a class.

Special Warnings to be included on the leaflet:
Only take this medicine to treat acute episodes of diarrhoea associated with Irritable Bowel Syndrome if your doctor has previously diagnosed IBS.

If any of the following now apply, do not use the product without first consulting your doctor, even if you know you have IBS:

- If you are aged 40 or over and it is some time since your last IBS attack
- If you are aged 40 or over and your IBS symptoms are different this time
- If you have recently passed blood from the bowel
- If you suffer from severe constipation
- If you are feeling sick or vomiting
- If you have lost your appetite or lost weight
- If you have difficulty or pain passing urine
- If you have a fever
- If you have recently travelled abroad

Consult your doctor if you develop new symptoms, if your symptoms worsen, or your symptoms have not improved over two weeks.

Information about excipients:

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

This medicine contains 5 mg aspartame in each orodispersible tablets. 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. Neither non-clinical nor clinical data are available to assess aspartame use in infants below 12 weeks of age.

This medicine contains saccharose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency 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, which are both P-glycoprotein inhibitors, resulted in a 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, 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 concentration 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 hydrochloride 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, dizziness, or drowsiness may occur when diarrhoea is treated with loperamide hydrochloride. 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 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 adverse drug reactions (i.e., ≥ 1 % incidence) in clinical trials with loperamide hydrochloride in acute diarrhoea were constipation (2.7 %), flatulence (1.7 %), headache (1.2 %) and nausea (1.1 %).

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

Table 1: Adverse Drug Reactions

System Organ Class	Indication			
	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]	Ileus[a] (including paralytic ileus) Megacolon[a] (including toxic megacolon[b]) 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]	

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 = 3,683).

[b] See section 4.4 Special Warnings and Special Precautions for use.

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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, ileus and urinary retention 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.

Upon cessation, cases of drug withdrawal syndrome have been observed in individuals abusing, misusing, or intentionally overdosing 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 gut wall, 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

Absorption

Most ingested loperamide 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 is 95%, mainly to albumin. Non-clinical data have shown that loperamide is a P-glycoprotein substrate.

Metabolism

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 comparisons (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 foetal health and did not affect peri- and post-natal development.

Non-clinical in vitro and in vivo evaluation of loperamide hydrochloride indicate 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

Croscarmellose sodium

Aspartame E951

Magnesium stearate

Mannitol

Fruit Flavour (contains Acacia gum E414, Sugar (saccharose), Maltodextrin (potato), Triacetin, Propylene glycol),

Banana Flavour (contains Maize maltodextrin)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

Orodispersible tablets are packaged in PVC / PVDC / Alu blister packs.

Pack sizes: 6 and 12 orodispersible tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Milpharm Limited
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Stockley Park,
Uxbridge,
UB11 1AF,
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PL 16363/0784

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

31/07/2023

10 DATE OF REVISION OF THE TEXT

21/05/2026