SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Loperamide 2 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 2 mg Loperamide Hydrochloride.

Excipient(s) with known effect:

This product contains lactose monohydrate

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard

Green and dark grey, size 4 capsules containing a fine white powder. Printed 'LOP2'.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Loperamide hydrochloride is indicated 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 over 8 years. Loperamide hydrochloride is also indicated for the symptomatic treatment of chronic diarrhoea in adults.

4.2. Posology and method of administration

For oral administration.
The capsules should be taken with liquid.

Acute diarrhoea

Adults and Children 8-17 years

The initial dose is 2 capsules (4 mg) for adults and 1 capsule (2 mg) for children; followed by 1 capsule (2 mg) after every subsequent loose stool.

The maximum dose is 8 capsules (16 mg) daily for adults; in children it must be related to the body weight (3 capsules/20 kg) but should not exceed a maximum of 8 capsules per day.

Chronic Diarrhoea

Adults
The initial dose is 2 capsules (4 mg) daily; this initial dose should be adjusted until 1-2 solid stools a day are obtained, which is usually achieved with a maintenance dose of 1-6 capsules (2 mg-12 mg) daily.
Tolerance has not been observed and therefore subsequent dosage adjustment should be unnecessary.

The maximum dose is 8 capsules (16 mg) daily.

Paediatric Populations

Children 2-8 years
The capsule form of loperamide is not recommended in children of this age. A syrup is commercially available.

Children Under 2 Years
Loperamide HCl should not be used in children under 2 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 loperamide HCl should be used with caution in such patients because of reduced first pass metabolism (see Section 4.4).

4.3 Contraindications

- Loperamide HCl is contraindicated in patients with a known hypersensitivity to loperamide HCl or to any of the excipients listed in section 6.1.
- Not to be used in children under 12 years of age.
- Loperamide HCl should not be used:
    - 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 HCl should not be used if inhibition of peristalsis is to be avoided due to the possible risk of significant sequelae including ileus, megacolon, toxic megacolon. Loperamide HCl must be discontinued promptly when constipation, abdominal distension or ileus develop.

4.4 Special warnings and precautions for use

Treatment of diarrhoea with loperamide HCl is only symptomatic. Whenever an underlying etiology can be determined, specific treatment should be given when appropriate.

In patients with diarrhoea, especially in children, fluid and electrolyte depletion may occur. The use of loperamide HCl does not preclude the need for appropriate fluid and electrolyte replacement therapy, which is essential in such patients. Loperamide HCl should not be given to children aged 2 to 6 years without medical prescription and supervision.

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 HCl should be discontinued and patients should be advised to consult their physician.

Patients with AIDS treated with loperamide HCl 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 HCl.

Although no pharmacokinetic data are available in patients with hepatic impairment, loperamide HCl should be used with caution in such patients because of reduced first pass metabolism**.** Patients with hepatic dysfunction should be monitored closely for signs of 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.

Caution is needed in patients with a history of drug abuse. Abuse and misuse of loperamide, has been described (see section 4.9). 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.

Excipients

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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

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 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, dizziness, or drowsiness may occur when diarrhoea is treated with loperamide HCl. Therefore, it is advisable to use caution when driving a car or operating machinery (see section 4.8).

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%).

List of adverse reactions

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); unknown (cannot be estimated from the available data).

Table 1: Adverse Drug Reactions

System Organ Class	**Indication**			
	Common	**Uncommon**	**Rare**	**Unknown**

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]	

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.

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, 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, 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

ATC Code: A07DA03 Antipropulsives.

Loperamide hydrochloride binds to the opiate receptor in the gut 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 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 hydrochloride.

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 high affinity for the gut wall with preference for binding to the receptors in 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 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 9-14 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 ($\geq$ 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 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

Capsules contain:

Maize starch

Lactose monohydrate

Povidone (E1201)

Sodium starch glycolate (Type A)

Magnesium Stearate (E572)

The capsule shell contains:

Gelatin

Patent blue V (E131)

Titanium dioxide (E171)

Yellow iron oxide (E172).

The printing ink contains:

Shellac

Simeticone

Titanium dioxide (E171)

Propylene glycol (E1520).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

HDPE containers with LDPE lids or polypropylene containers with polyethylene lids in packs of 100, 250 and 500 capsules.

PVdC coated PVC film with hard temper aluminium foil strips in packs of 30 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

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

7 MARKETING AUTHORISATION HOLDER

Teva UK Limited,
Ridings Point,
Whistler Drive,
Castleford,
WF10 5HX,
United Kingdom.

8 MARKETING AUTHORISATION NUMBER(S)

PL 00289/1980

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/01/2025

10 DATE OF REVISION OF THE TEXT

21/01/2025