1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

Enclosed.

BRAND NAME:	**DIARRAX**
GENERIC NAME:	**LOPERAMIDE CAPSULE 2 MG**

Summary Product Characteristics

1. Name of the proprietary product: DIARRAX

Name of the non-proprietary International Product: Loperamide Capsule BP 2 mg

Route of Administration: Oral

2. Qualitative and Quantitative composition:

Sr. No.	Ingredients	Specifications	Quantity / capsule (mg)	Label Claim	Reason for inclusion
1.	Loperamide Hydrochloride	BP	2.00	2.00	Active
2.	Lactose	BP	50.00	--	Diluent
3.	Microcrystalline Cellulose	BP	22.50	--	Lubricant
4.	Maize Starch	BP	141.50	--	Diluent
5.	Croscarmellose Sodium	BP	7.00	--	Disintegrant
6.	Colloidal Silicon Dioxide	BP	2.00	--	Glidant
8.	E.H.G-4 Grey/green	IH	1 No.	--	Capsule Shell

BP= British Pharmacopoeia,

IH= In-House

3. Pharmaceutical Form: Capsule for oral administration.

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:

Acute Diarrhoea

Adults and children aged 12 years and over:

The initial dose is 2 capsules (4 mg), followed by 1 capsule after every subsequent loose stool. The usual dose is 3-4 capsules (6-8 mg) a day. The total daily dose should not exceed 6 capsules (12 mg).

Paediatric population

Not to be given to children under 12 years of age.

Symptomatic treatment of acute episodes of diarrhoea associated with irritable bowel syndrome in adults aged 18 years and over

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

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 pharmacokinetics data is available in patients with hepatic impairment, loperamide should be used with caution in such patients because of reduced first pass metabolism.

Method of administration

For oral use. The capsules should be swallowed 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 under the age of 12 years old.

• 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 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 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. 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.

Persistent diarrhoea can be an indicator of potentially more serious conditions and as such loperamide 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 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 should be used with caution in such patients because of reduced first pass metabolism. This medicine must be used with caution in patients with hepatic impairment as it may result in a relative overdose leading to CNS toxicity.

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

Cardiac events including QT prolongation and torsades de pointes have been reported in association with overdose. Some cases had a fatal outcome. Patients should not exceed the recommended dose and/or the recommended duration of treatment.

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.

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

<u>Pregnancy</u>

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

Breastfeeding

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

Women who are pregnant or breast-feeding 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 the 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 exercise caution when operating machinery or driving a car following administration of loperamide HCl

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%).

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); 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], depressed level of consciousness[a], hypertonia[a], coordination abnormality
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
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 differentiated 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).

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), urinary retention, constipation 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 prolongation, torsades de pointes, other serious ventricular arrhythmias, cardiac arrest and syncope have been observed. Fatal cases have also been reported.

Management:

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 any possible CNS depression.

5. Pharmacological Particulars:

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antipropulsives: ATC code A07DA03

By binding to opiate receptors in the gut wall, loperamide hydrochloride reduces propulsive peristalsis, increases intestinal transit time and enhances 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 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.

Paediatric population

No pharmacokinetic studies were performed in the paediatric population. It is expected that pharmacokinetic behaviour of loperamide and drug-drug interactions with loperamide will be similar to those in adults.

5.3 Pre-clinical Safety:

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/m2) loperamide impaired fertility and fetal survival in association with maternal toxicity in rats. Lower doses (≥10mg/kg/day – 5 times MHUL) had 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, loperamide has cardiac electrophysiological actions consisting of inhibition of potassium (hERG) and sodium currents, and arrhythmias.

6. Pharmaceutical Particulars:

6.1 List of Excipients:

Maize Starch	BP
Purified Talc	BP
Sodium Starch Glycolate	BP
Sodium Lauryl Sulfate	BP
Colloidal Silicon Dioxide	BP
Lactose	BP
E.H.G-2 Scarlet red- White	IH

6.2 Incompatibilities:

None known.

6.3 Shelf Life:

36 months.

6.4 Special Precautions for storage:

No special precautions for storage.

6.5 Nature and contents of container:

1 Alu-PVC Blisters of 10 capsules to be packed in printed inner carton along with the Pack Insert and such a 10 inner carton to be packed in outer carton.

6.6 Special precautions for disposal and other handling:

No special requirements.

7. Marketing Authorization Holder:

LESANTO LABORATORIES

PLOT NO, 9, 10, 11,

SURVEY NO.53,

PALGHAR (E) -401 404,

MAHARASHTRA,

INDIA

8. Marketing Authorization Number: ---

9. Date of first Authorization /renewal of the authorization: ---

10. Date of revision of text: Jan. 2020