1. Name of the Medicinal Product

1.1 Name of the Medicinal Product

DIAFLUSH CAPSULES (Loperamide Hydrochloride Capsules USP 2 mg)

1.2. Strength

Loperamide Hydrochloride	USP	2 mg
Excipients		q.s.

1.3. Pharmaceutical Dosage Form

Solid dosage form (Capsules)

2. Qualitative And Quantitative Composition

Qualitative Declaration

DIAFLUS CAPSULES contains Loperamide Hydrochloride.

Quantitative Declaration

Each hard gelatin capsule contains:

Loperamide Hydrochloride	USP	2 mg
Excipients		q.s.

Approved colour used in empty capsule shells.

3. Pharmaceutical Form

Solid dosage form (Capsule)

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 over 12:

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

SYMPTOMATIC TREATME NT 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).

PAEDIATRIC POPULATION

Diaflush Capsules are contraindicated in children less than 12 years of age.

USE IN 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, Diaflush Capsules should be used with caution in such patients because of reduced first pass metabolism.

Method of administration is for oral use. The capsule should be taken with liquid.

4.3 Contraindications

Diaflush Capsules are contraindicated:

• in patients with a known hypersensitivity to loperamide hydrochloride or to any of the excipients listed.

• 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.

Diaflush Capsules 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. Diaflush Capsules must be discontinued promptly when ileus, constipation or abdominal distension develops.

4.4 Special Warning and Precautions for Use

Treatment of diarrhoea with Diaflush Capsules 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 Diaflush Capsules 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.

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, 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.

Special Warnings to be included on the leaflet:

Only take Diaflush Capsules 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.

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 posseses any teratogenic or embryotoxic properties. As with other drugs, it is not advisable to administer Diaflush Capsules in pregnancy, especially in the first trimester.

Breastfeeding

Small amounts of loperamide may appear in human breast milk. Therefore, Diaflush Capsules 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.

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 this medicine. Therefore, it is advisable to use caution when driving a car or operating machinery.

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 display 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: Adverse Drug Reactions

System Organ Class	**Indication**		
	Common	**Uncommon**	**Rare**
Immune System Disorders			Hypersensitivity reaction Anaphylactic reaction (including Anaphylactic shock) Anaphylactoid reaction
Nervous System Disorders	Headache	Dizziness Somnolence	Loss of consciousness Stupor[a] Depressed level of Consciousness[a] Hypertonia Coordination abnormality
Eye Disorders			Miosis
Gastrointestinal Disorders	Constipation Nausea Flatulence	Abdominal pain Abdominal discomfort Dry mouth Abdominal pain upper Vomiting Dyspepsia	Ileus (including paralytic ileus) Megacolon (including toxic megacolon) Abdominal distension
Skin and Subcutaneous Tissue Disorders		Rash	Bullous eruption (including Stevens- Johnson syndrome, Toxic epidermal necrolysis and Erythema multiforme) Angioedem

			Urticaria Pruritus
Renal and Urinary Disorders			Urinary retention
General Disorders and Administration Site Conditions			Fatigue

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).

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, 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.

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.

5.0 Pharmacological Properties

ATC code: A07DA03

5.1 Pharmacodynamic properties

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 randomized 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 anti-diarrhoeal 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/m2), loperamide impaired fertility and fetal 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, 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
- Calcium Hydrogen Phosphate BP
- Lactose BP
- Magnesium Stearate BP
- Purified Talc BP

x Colloidol Silicon Dioxide BP

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

36 Months

6.4 Special Precautions for Storage

Store in a dry place at a temperature below 25°C. Protect from light.

Keep all medicines out of reach of children.

6.5 Nature and Contents of Container

1 x 10 Capsules are packed in a unit carton along with patient information leaflet.

6.6 Special Precautions for Disposal and Other Handling

No special requirements for disposal.

7. Registrant/Sole Agent

EMBASSY PHARMACEUTICAL & CHEMICAL LTD.

41, Ademola Street, South West Ikoyi,

Lagos, Nigeria.Tel.: 01-2900791

8. Manufacturer

LABORATE PHARMACEUTICALS INDIA LIMITED

31, Rajban road, Nariwala, Paonta Sahib, District-Sirmour,

Himachal Pradesh (INDIA)

H.O.: E-11, Indl. Area, Panipat-132103

laborate@laborate.com

9. Date of Revision of Text

To be given after approval of product.

10. Dosimetry (If applicable)

Not applicable

11. Instructions for Preparation of Radiopharmaceuticals (If applicable)

Not applicable