For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

LOPAMIDE

1. Generic Name

Loperamide Hydrochloride Tablets I.P.

2. Qualitative and quantitative composition

Each uncoated tablets contains:

Loperamide Hydrochloride I.P….2mg

The other excipients are Lactose Monohydrate, Polyvinyl Pyrrolidone, Talc, Colloidal Silicon Dioxide, Starch Dried and Magnesium Stearate.

3. Dosage form and strength

Dosage Form: Tablets

Strength: 2 mg

4. Clinical particulars

4.1 Therapeutic indication

Indicated in the treatment of acute diarrhoea due to food poisoning, viral infections.

4.2 Posology and method of administration

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

Method of administration

Oral use. The tablets should be taken with liquid. Not to be administered in children below 12 years.

4.3 Contraindications

This medicine is contraindicated:

- hypersensitivity to the active substance or to any of the excipients
- 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.

LOPAMIDE 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.

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

4.4 Special warnings and precautions for use

Treatment of diarrhoea with LOPAMIDE 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 LOPAMIDE 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 torsades de pointes have been reported in association with overdose. Some cases had a fatal outcome. Overdose can unmask existing Brugada syndrome. Patients should not exceed the recommended dose and/or the recommended duration of treatment.

4.5 Drugs interactions

Reported 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 Pglycoprotein 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.

Reportedly, 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).

As per another reported study, 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, states a reported study.

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

4.8 Undesirable effects

Adults and children aged ≥ 12 years

Reportedly, 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 reported 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	**Indication**		
	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[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 toxicmegacolon[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 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 side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

By reporting side effects, you can help provide more information on the safety of this medicine.

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.

Reportedly, 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.

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.

5.1 Mechanism of Action

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.

5.2 Pharmacodynamic properties

Pharmacotherapeutic Group: Antipropulsives; ATC code: A07DA03

In a reported 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.

5.3 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: Reported 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.

6. Nonclinical properties

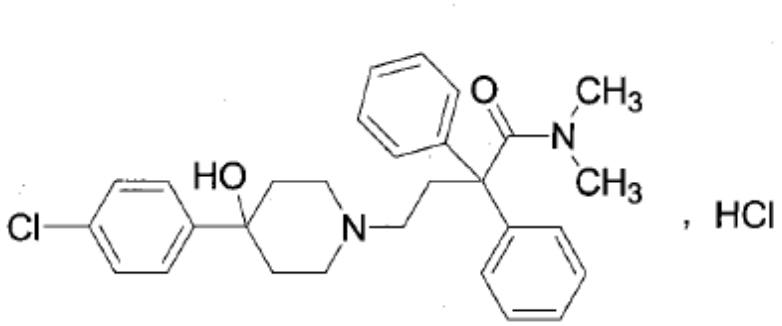
6.1. Animal Toxicology or Pharmacology

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

7. Description

The chemical name of Loperamide Hydrochloride is 4-(4-chlorophenyl)-4-hydroxypiperidino]-N ,N-dimethyl-2,2-diphenylbutyramide hydrochloride (IUPAC). Its molecular formula is $C_{29}H_{33}ClN_2O_2$,HCl and its molecular weight is 513.50. The chemical structure is:



Loperamide is a white or almost white powder. It is Freely soluble in methanol; soluble in ethanol (95 per cent); slightly soluble in water.

Product Description:

White to off-white, round, flat uncoated beveled edge tablet debossed with “LOPAMIDE” on one side and cross line on other side.

8. Pharmaceutical particulars

8.1. Incompatibilities

None stated

8.2. Shelf-life

Do not use later than the date of expiry

8.3. Packaging information

LOPAMIDE is available in 15 COMPOSITE PACKS OF 5 X 10 TABLETS EACH.

8.4. Storage and handing instructions

Store at a temperature not exceeding 30°C, protected from light and moisture. Not to be administered in children below 12 years.

9. Patient counselling information

LOPAMIDE

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet?

9.1. What LOPAMIDE is and what it is used for

LOPAMIDE is used to treat diarrhoea.

LOPAMIDE contains loperamide hydrochloride, a substance that helps reduce diarrhoea by slowing down an overactive bowel. This allows water and salts that are usually lost in diarrhoea to be absorbed by the body.

9.2. What you need to know before you take LOPAMIDE Warnings for everyone

This medicine is suitable for most people, but a few people should not use it:

Do not take this medicine…

- If you have ever had **a bad reaction** to any of the ingredients.
- If it is for a child aged **under 12**.
- If you have **severe diarrhoea** after taking **antibiotics**.
- If you are having a flare-up of an **inflammatory bowel condition** like **ulcerativecolitis.**
- If you are **constipated**, or your **stomach appears swollen** (especially in children with severe dehydration).
- If you have **acute dysentery**, the symptoms of which may include **blood in your stools and a high temperature.**

If any of these applies to you, talk to a doctor **and do not take LOPAMIDE. Warnings for everyone (continued)**

Talk to your doctor first…

- If you have **AIDS** and your **stomach becomes swollen**, stop taking LOPAMIDE

immediately and contact your doctor.

- If you suffer from **liver disease.**
- If you have diarrhoea that lasts for **more than 48 hours**.
- If you have been told by your doctor that you have an **intolerance to some sugars.**
- If you have **severe diarrhoea** as your body loses more fluid, sugars and salts than normal.
- If you are taking any **other medicines**, including:
    - ritonavir (used to treat **HIV)**.
    - quinidine (used to treat **abnormal heart rhythms** or **malaria**).
    - oral desmopressin (used to treat **excessive urination**).
    - Iitraconazole or ketoconazole (used to treat **fungal infections**).
    - gemfibrozil (used to treat **high cholesterol**).

If any of these applies to you (now or in the past), **talk to a doctor**. **Pregnancy or breastfeeding**

- **If you are pregnant**, think you are pregnant or planning a pregnancy: ask your doctor or pharmacist for advice before taking this medicine.
- **If you are breast-feeding** do not take this medicine. Small amounts may get into your milk. Talk to your doctor about a suitable treatment.

Driving and using machines

- This medicine may make you feel dizzy, tired or sleepy. You may feel less alert, feel faint or pass out. If you're affected do not drive, cycle or use machines.

Special warnings about this medicine

- Your body can lose large amounts of fluids and salts when you have diarrhoea. You need to replace the fluid by drinking more liquid than usual. Ask your pharmacist about rehydration therapy to replace lost salts. This is especially important for children, and frail or older people.
- Do not take this product for anything other than its intended use (see section 9.1) and never take more than the recommended amount.Serious heart problems (symptoms of which include fast or irregular heartbeat) have been reported in patients who have taken too much loperamide, the active ingredient in LOPAMIDE.

Some of the ingredients can cause problems

- This medicine contains lactose. If you have been told by your doctor that you have an intolerance to some sugars contact your doctor before taking this medicine.

9.3. How to take LOPAMIDE

Always take this medicine exactly as described in this leaflet or as your doctor or pharmacist has told you. Check with your doctor if you are not sure.

Check the tables below to see how much medicine to take.

- Swallow the correct number of tablets whole with a drink of water. For oral use only.
- Do not use more than the dose shown in the tables.

- The tablets are not for long-term treatment.

Short-term diarrhoea

Age	**Dose**
Adults and children aged 12 and over	**Take two tablets to start treatment.**
	Take one tablet after each loose bowel movement.

- Do not take for attacks lasting longer than 48 hours.
- Do not take more than six tablets in a 24-hour period.
- Replace lost fluid by drinking more liquid than usual.
- Not for children aged under 12.

How long to take LOPAMIDE

You can use this medicine for up to 48 hours.

If your attack lasts longer than 48 hours, stop taking LOPAMIDE and talk to your doctor.

If you take too much of this medicine

If you have taken too many LOPAMIDE, immediately contact a doctor or hospital for advice. Symptoms may include: increased heart rate, irregular heartbeat, changes to your heartbeat (these symptoms can have potentially serious, life-threatening consequences), muscle stiff ness, uncoordinated movements, drowsiness, difficulty urinating, or weak breathing.

Children react more strongly to large amounts of LOPAMIDE than adults. If a child takes too much or shows any of the above symptoms, call a doctor immediately.

If you forget to take the medicine

You should only take this medicine as you need it, following the dosage instructions above carefully.

If you forget to take a dose, take a dose after the next loose stool (bowel movement). Do not take a double dose.

9.4. Possible side effects

LOPAMIDE can have side effects, like all medicines, although these don't affect everyone and most are usually mild.

Get medical help at once

Rare: (may affect up to 1 in 1,000 people)

- Allergic reactions including unexplained wheezing, shortness of breath, passing out or swelling of face and throat.
- Skin rashes, which may be severe and include blistering or peeling skin.
- Loss of consciousness or reduced level of consciousness (passing out, feeling faint or less alert), uncoordinated movements.

If you get any of these, **stop using the medicine and get medical help at once.**

Talk to a doctor as soon as possible Uncommon: (may affect up to 1 in 100 people)

- Itchiness or hives.
- Stomach pain or swollen stomach.

Rare: (may affect up to 1 in 1,000 people)

- Difficulties passing water.
- Severe constipation.
- Miosis (narrowing of the pupils of the eye).

If you notice any of the above, stop using the medicine and **talk to a doctor**. **Other effects that may occur**

Common: (may affect up to 1 in 10 people)

- Feeling sick, constipation or wind.
- Headache.

Uncommon: (may affect up to 1 in 100 people)

- Dizziness or drowsiness.
- Vomiting, indigestion.
- Dry mouth.

Rare: (may affect up to 1 in 1,000 people) Tiredness.

9.5. How to store LOPAMIDE

Store at a temperature not exceeding 30°C, protected from light and moisture.

9.6. Contents of the pack and other information

LOPAMIDE contains Loperamide Hydrochloride I.P. 2mg as an active ingredient.

The other inactive ingredients are Lactose Monohydrate, Polyvinyl Pyrrolidone, Talc, Colloidal Silicon Dioxide, Starch Dried and Magnesium Stearate.

10. Details of Manufacturer

TORRENT PHARMACEUTICALS LTD.

32 No., Middle Camp, NH-10,

East District, Gangtok, Sikkim-737 135

OR

Innova Captab Limited

Kh No. 1281/1, Hilltop, Industrial Estate,

Nr. EPIP, Phase-1, Jharmajri,

Baddi, Distt. Solan (H.P.)-173205.

11. Details of permission or licence number with date

Mfg Lic No.: M/563/2010 issued on 06.12.2021

OR

License No.: MNB/16/970 issued on 04.01.2021

12. Date of revision

Sep-2022

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/LOPAMIDE 2 mg/ Sep 2022/05/PI