



**MASCOT HEALTH SERIES PRIVATE LIMITED
HARIDWAR, UTTARAKHAND, INDIA**

1.3.1 Name of the medicinal product

1.3.1.1 Product name

Loperamide Hydrochloride Capsules USP 2 mg

1.3.1.2 Strength

2 mg

1.3.1.3 Pharmaceutical Dosage Form

Hard Gelatin capsule

1.3.2 Qualitative and quantitative composition

1.3.2.1 Qualitative Declaration

Label Claim:

Composition:

Each Hard Gelatin capsule contains:

Loperamide Hydrochloride USP 2 mg

Excipients q.s.

Approved colour used in empty capsule shells.

1.3.2.2 Quantitative Declaration

2 mg/ Capsule

1.3.2.3 Pharmaceutical form

Hard Gelatin capsule (Capsule)

1.3.2.4 Clinical particulars

Therapeutic indications

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 9 years. For the symptomatic treatment of chronic diarrhoea in adults.

1.3.2.5 Posology and method of administration

Posology

Acute diarrhoea

Adults and children over 12 years

Two Capsules(4 mg) initially, followed by one Capsules(2 mg) after every loose stool. The usual dosage is 3-4 Capsules(6 mg-8 mg) per day. The maximum daily dose should not exceed 8 Capsules(16 mg).

Children 9 to 12 years

One Capsules (2 mg) four times daily until diarrhoea is controlled (up to 5 days). This dose should not be exceeded.

Further investigation into the cause of the diarrhoea should be considered if there is no improvement within two days of starting treatment with loperamide.

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Chronic diarrhoea Adults

Patients may need widely differing amounts of loperamide. The starting dose should be between two and four Capsules per day in divided doses, depending on severity. If required, this dose can be adjusted according to result up to a maximum of eight Capsules daily.

Having established the patient's daily maintenance dose, loperamide may be administered on a twice daily regimen. Tolerance has not been observed and therefore subsequent dosage adjustment should be unnecessary.

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 should be used with caution in such patients because of reduced first pass metabolism

Method of administration

Oral use. The Capsules should be taken with liquid.

1.3.3 Contraindications

Loperamide is contraindicated in:

- patients with a known hypersensitivity to loperamide hydrochloride or to any of the excipients listed in section 6.1.
- children less than 9 years of age.
- Loperamide should not be used as the primary therapy:
 - o patients with acute dysentery, which is characterised by blood in stools and high fever.
 - o patients with acute ulcerative colitis.
 - o patients with bacterial enterocolitis caused by invasive organisms including Salmonella, Shigella and Campylobacter.
 - o patients with pseudomembranous colitis associated with the use of broad-spectrum antibiotics.

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

1.3.4 Special warnings and precautions for use

Treatment of diarrhoea with loperamide 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 loperamide hydrochloride does not preclude the administration of appropriate fluid and electrolyte replacement therapy.

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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.

Loperamide hydrochloride must be used with caution when the hepatic function necessary for the drug's metabolism is defective (eg in cases of severe hepatic disturbance), as this might result in a relative overdose leading to CNS toxicity

Patients with AIDS treated with loperamide hydrochloride for diarrhoea should have therapy stopped at the earliest signs of abdominal distension. There have been isolated reports of toxic megacolon in AIDS patients with infectious colitis from both viral and bacterial pathogens treated with loperamide hydrochloride.

When no clinical change is observed in the acute diarrhoea within 48 hours, the administration of loperamide must be interrupted and the patient must be advised to consult his doctor.

Treatment with Loperamide must be interrupted immediately when obstipation, abdominal distension or subileus develops

Cardiac events including QT 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.

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.

1.3.5 Interaction with other medicinal products and other forms of interaction

Non-clinical data have shown that loperamide is a P-glycoprotein substrate. Furthermore, loperamide is mainly metabolised by CYP3A4 and CYP2C8. 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 results of one published pharmacokinetic study suggested that the concomitant administration of loperamide with oral desmopressin may result in a 3-fold increase of desmopressin plasma concentrations although no clinical effects were reported.

Possible interactions may occur with drugs that delay intestinal peristalsis (for instance anticholinergic drugs) because the effects of loperamide could be enhanced.

Administration of itraconazole with loperamide (4 mg single dose) increased loperamide plasma levels 3- to 4-fold. In addition, gemfibrozil, a CYP2C8 inhibitor, increased the AUC of loperamide 2-fold. Concomitant use of itraconazole and gemfibrozil with loperamide raised the mean C_{max} and AUC of loperamide about 2- and 13-fold, respectively. This increase did not lead to measurable CNS effects.

The concomitant administration of loperamide (16mg single dose) and ketoconazole, an inhibitor of CYP3A4 and p-glycoprotein, resulted in a 5-fold increase in loperamide plasma

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concentrations. This increase was not associated with increased pharmacodynamic effects as measured by pupillometry.

The clinical relevance of these pharmacokinetic interactions, when loperamide is given at recommended dosages (2 mg, up to 12 mg maximum daily dose), is unknown

1.3.6 Fertility, pregnancy and lactation

Pregnancy

A limited amount of data from the use of loperamide in pregnant women is available. In one of two epidemiological studies the use of loperamide during early pregnancy suggested a possible moderate increased risk for hypospadias, however, an increased risk for major malformations could not be identified. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). 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.

If possible the use of loperamide should be avoided during the first trimester of pregnancy, however, it may be used during the second and third trimester of pregnancy

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

Only high doses of loperamide hydrochloride affected female fertility in non-clinical studies

1.3.7 Effects on ability to drive and use machines

Loperamide hydrochloride has moderate influence 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 hydrochloride.

Therefore, it is advisable to use caution when driving or operating machinery. (See section 4.8 Undesirable effects).

1.5.8 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 (i.e. $\geq 1\%$ incidence) adverse drug reactions (ADRs) in clinical trials with loperamide hydrochloride 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 hydrochloride from either clinical trial (acute diarrhoea) or post-marketing experience.

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The frequency categories use the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); and very rare ($< 1/10,000$).

Table 1 Adverse Drug reactions

System Organ Class	Indication		
	Common	Uncommon	Rare
<i>Immune System Disorders</i>			Hypersensitivity reaction ^a Anaphylactic reaction (including Anaphylactic shock) ^a Anaphylactoid reaction ^a
<i>Nervous System Disorders</i>	Headache Dizziness	Somnolence ^a	Loss of consciousness ^a Stupor ^a Depressed level of consciousness ^a Hypertonia ^a Coordination abnormality ^a
<i>Eye Disorders</i>			Miosis ^a
<i>Gastrointestinal Disorders</i>	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) Glossodynia ^a Abdominal distension
<i>Skin and Subcutaneous Tissue Disorders</i>		Rash	Bullous eruption ^a (including Stevens-Johnson syndrome, toxic epidermal Necrolysis and erythema multiforme) Angioedema ^a Urticaria Pruritus
<i>Renal and Urinary Disorders</i>			Urinary retention ^a
<i>General Disorders and Administration Site Conditions</i>			Fatigue ^a

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a: Inclusion of this term is based on 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=3683).

1.3.9 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 and ileus may occur. Children may be more sensitive to CNS effects than adults.

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 (see section 4.4). Fatal cases have also been reported. Overdose can unmask existing Brugada syndrome.

Treatment

If 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.

1.3.10 Pharmacological properties

1.3.10.1 Pharmacodynamic properties

General properties

Pharmacotherapeutic Group: Antipropulsives; ATC code: A07DA03

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.

Clinical efficacy and safety

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.

1.3.10.2 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.

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Biotransformation: 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.

1.3.11 Preclinical safety data

In high-dose animal studies, giving active substance concentrations 40-fold higher than those Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

Acute and chronic studies on loperamide showed no specific toxicity.

Loperamide had no effect on fertility in male rats when administered orally prior to mating at doses up to approximately 40 mg/kg. No pregnancy occurred in females dosed with approximately 40 mg/kg. Lower doses (approximately 10 and 2.5mg/kg) did not affect female

fertility. In rabbits no differences in pregnancy rate were observed when females were administered orally up to 40mg/kg.

No malformations of offspring were noted in rats and rabbits dosed up to 40 mg/kg. Loperamide did not show genotoxic potential.

In an 18-month carcinogenicity study in rats, with doses up to 100 times the maximum human dose no evidence of carcinogenesis was found.

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.



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1.3.12 Pharmaceutical particulars

1.3.12.1 List of excipients

Lactose monohydrate
Corn starch
Povidone K 30
Microcrystalline Cellulose pH-102
Corn starch
Sodium Starch Glycolate
Magnesium stearate
Purified water
Empty Hard Gelatin capsule Green/ Green "2"

1.3.13 Incompatibilities

Not applicable.

1.3.14 Shelf life

36 months.

1.3.15 Special precautions for storage:

Preserve in tight container. Store at controlled room temperature.

1.3.16 Nature and contents of container

Loperamide Hydrochloride Capsules USP 2 mg (50 x 4)

1.3.17 Marketing Authorization Holder:

MASCOT HEALTH SERIES PVT.LTD.

1.3.18 Marketing Authorization Numbers:

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1.3.19 Date of first authorization/renewal of the authorization:NA

1.3.20 Date of revision of the text:

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