

PACKAGE INSERT TEMPLATE FOR LOPERAMIDE HYDROCHLORIDE CAPSULE & TABLET

Brand or Product Name

[Product name] Tablet 2mg

[Product name] Capsule 2mg

Name and Strength of Active Substance(s)

Loperamide hydrochloride ...mg

Product Description

[Visual description of the appearance of the product (eg colour, markings etc)]

eg White, circular flat beveled edge tablets marked '2' on one side

Pharmacodynamics

Loperamide is a synthetic derivative of pethidine that inhibits gut motility and may also reduce gastrointestinal secretions.

Loperamide binds to the opiate receptor in the gut wall. Consequently, it inhibits the release of acetylcholine and prostaglandins, thereby reducing propulsive peristalsis, and increasing intestinal transit time. Loperamide increases viscosity, increases bulk density, reduces daily fecal volume, and diminishes loss of fluids and electrolytes. Loperamide increases the tone of the anal sphincter, thereby reducing incontinence and urgency. Additionally, loperamide will prolong mouth-to-cecum transit time without affecting gastric emptying.

Pharmacokinetics

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:

Little intact drug reaches the systemic circulation

Gastrointestinal tract: 85%

Liver: 5%

Tissues: 0.04 to 0.2%

The plasma protein binding of loperamide is 95%, mainly to albumin.

Metabolism:

Loperamide undergoes significant first pass metabolism in the liver. Oxidative N-demethylation is the main metabolic pathway for loperamide, and is mediated mainly through CYP3A4 and CYP2C8. Oxidative n-dealkylation may be another pathway. 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 10.8 hours with a range of 9-14 hours. Approximately 50% of an orally administered dose is excreted unchanged, primarily in the faeces; there is slight urinary excretion

Indication

Loperamide HCl is indicated for the symptomatic control of acute and chronic diarrhea. In patients with an ileostomy it can be used to reduce the number and volume of stools and to harden their consistency.

Recommended Dosage

Adult

Acute diarrhoea: the initial dose is 4 mg; followed by 2 mg after every subsequent loose stool.

Chronic diarrhoea: the initial dose is 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 2 mg - 12 mg daily.

The maximum dose for acute and chronic diarrhoea is 16 mg daily for adults;

Paediatric

Acute diarrhoea

Below 6 years old: The use of loperamide in children under 6 years is not recommended.

6 to 8 years old: 4 mg per day in divided doses

9 to 12 years old: 6 mg per day in divided doses

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.

Mode of Administration

Oral

Contraindications

Loperamide HCl is contraindicated in patients with a known hypersensitivity to loperamide HCl or to any of the excipients.

Loperamide HCl should not be used in children under 2 years

Loperamide HCl should not be used as the primary therapy:

- in patients with acute dysentery, which is characterized 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 when inhibition of peristalsis is to be avoided due to the possible risk of significant sequelae including ileus, megacolon and toxic megacolon.

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

Warnings and Precautions

[Specific package insert requirement for Loperamide]

WARNING:

Not recommended for children under 6 years of age. Its use has been associated with fatal episodes of paralytic ileus in infants and young children.

PRECAUTION:

Appropriate fluid and electrolyte therapy should be given to protect against dehydration in all cases of diarrhoea. Oral rehydration therapy which is the use of appropriate fluids including oral rehydration salts remains the most effective treatment for dehydration due to diarrhoea. The intake of as much of these fluids as possible is therefore imperative. Drug-induced inhibition of peristalsis may result in fluid retention in the intestine, which may aggravate and mask dehydration and depletion of electrolytes. If severe dehydration or electrolyte imbalance is present Loperamide should be withheld until appropriate corrective therapy has been initiated.

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

In acute diarrhea, 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 diarrhea should have therapy stopped at the earliest signs of abdominal distension. There have been isolated reports of constipation 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. This medicine must be used with caution in patients with hepatic impairment as it may result in a relative overdose leading to CNS toxicity.

Effects on Ability to Drive and Use Machines

Tiredness, dizziness, or drowsiness may occur in the setting of diarrheal syndromes treated with loperamide HCl. Therefore, it is advisable to use caution when driving a car or operating machinery.

Interactions with Other Medicaments

Concomitant administration of loperamide with *quinidine*, or *ritonavir*, which are both P-glycoprotein inhibitors, resulted in a 2 to 3-fold increase in loperamide plasma levels.

Saquinavir

Interaction Effect: decreased saquinavir plasma concentrations, and increased loperamide plasma concentrations

Coadministration of loperamide and saquinavir significantly decreases saquinavir C_{max} and AUC, possibly due to impaired absorption of saquinavir caused by the effect of loperamide to the gastrointestinal tract. Due to the possibility of reduced antiviral efficacy of saquinavir, their concomitant use should be avoided, especially for prolonged therapy. There is also an increase in the exposure of loperamide, although it is unlikely to be clinically significant

The concomitant administration of loperamide and *itraconazole*, an inhibitor of CYP3A4 and P-glycoprotein, resulted in a 3 to 4-fold increase in loperamide plasma concentrations.

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.

The concomitant administration of loperamide and *ketoconazole*, an inhibitor of CYP3A4 and P-glycoprotein, resulted in a 5-fold increase in loperamide plasma concentrations.

Concomitant treatment with oral *desmopressin* resulted in a 3-fold increase of desmopressin plasma concentrations, presumably due to slower gastrointestinal motility.

St John's Wort

Interaction Effect: delirium with symptoms of confusion, agitation, and disorientation

Valerian

Interaction Effect: delirium with symptoms of confusion, agitation, and disorientation

Co-trimoxazole

Use with co-trimoxazole increases the bioavailability of loperamide apparently by inhibiting its first-pass metabolism.

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.

Statement on Usage During Pregnancy and Lactation

Pregnancy

Loperamide is poorly absorbed from the gut. Information is limited, but available data indicate it presents a minimum risk of malformations when used during pregnancy. However, due to the limited data, its therapeutic benefits should be weighed against potential risk to the fetus when given during pregnancy, especially during the first trimester.

Lactation

The weight of an adequate body of evidence and/or expert consensus suggests this drug poses minimal risk to the infant when used during breastfeeding. Loperamide is distributed into breast milk in amounts probably too small to be harmful.

Adverse Effects / Undesirable Effects

Dermatologic Effects: Skin rash, Erythema multiforme, rash, Stevens-Johnson syndrome, Toxic epidermal necrolysis, urticaria, angioedema

Endocrine/Metabolic Effects: Hyperglycemia

Gastrointestinal Effects: appendicitis, bowel obstruction, constipation, flatulence, gallstone, gastrointestinal tract finding, indigestion, necrotizing enterocolitis in fetus or newborn, paralytic ileus, toxic megacolon, epigastric pain, nausea, dry mouth, vomiting, abdominal cramps, anorexia

Immunologic Effects: hypersensitivity reactions including anaphylactic shock and anaphylactoid reactions

Neurologic Effects: delirium, dizziness, fatigue, irritability, drowsiness, extrapyramidal reactions (acute dystonia, akathisia, pseudo-parkinsonism, tardive dyskinesia)

Renal Effects: urinary retention and increased urethral pressure

Overdose and Treatment

Symptoms

Common overdose effects: miosis, drowsiness, nausea, vomiting, abdominal pain, and headache. Seizures, dystonic reactions, ileus and pancreatitis have also occurred following overdose.

Treatment

Naloxone is an effective reversal agent. Initial dose of 2.0 mg intravenously; repeat as necessary. Patient should be monitored closely to detect possible CNS depression.

Storage Conditions

[eg Store below.... °C]

Dosage Forms and Packaging Available

[Packaging type & pack size]

Name and Address of Manufacturer

[Name & full address of manufacturer]

Name and Address of Marketing Authorization Holder

[Name & full address of marketing authorization holder]

Date of Revision of Package Insert

[day/month/year]