

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Loperamide Hydrochloride Capsules 2 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Loperamide hydrochloride 2mg For
excipients, see 6.1

Contains lactose 100mg per capsule

3 PHARMACEUTICAL FORM

Size 4, green opaque cap and a mauve opaque body, hard gelatin capsule marked "LOPERA-MIDE 2" on the cap.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Loperamide is indicated for the symptomatic treatment of acute diarrhoea of any aetiology including acute exacerbation of chronic diarrhoea for periods of up to 5 days, in adults and children over 4 years, and chronic diarrhoea in adults. Since persistent diarrhoea can be an indicator of potentially more serious conditions, Loperamide should not be used for prolonged periods until the underlying cause of the diarrhoea has been investigated.

4.2 Posology and method of administration

Loperamide hydrochloride capsules 2mg are for oral administration. The capsules should be taken with liquid.

Acute diarrhoea:

Adults: two capsules initially, followed by 1 capsule after every loose stool, for up to 5 days. The usual dosage is 3 to 4 capsules a day; the maximum daily dose should not exceed 8 capsules.

Children:

9-12 years: the maximum dose is 1 capsule 4 times daily until diarrhoea is controlled, for up to 5 days.

4-8 years: Loperamide hydrochloride capsules 2mg cannot be divided and are therefore not recommended for use in children aged 4-8 years. A suitable alternative presentation of loperamide should be used in these patients.

If there is no improvement within 2 days of starting treatment further investigation of the cause of diarrhoea should be considered.

Chronic diarrhoea:

Adults: studies have shown that patients may need widely differing amounts of loperamide hydrochloride. The starting dose should be between 2 and 4 capsules per day in divided doses, depending on severity. If required, this dose can be adjusted according to response. The maximum recommended daily dose is 8 capsules.

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

Children: loperamide is not recommended for treatment of chronic diarrhoea in children

Use in elderly: acute and chronic diarrhoea - as for adults

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 hydrochloride should be used with caution in such patients because of reduced first pass metabolism (see section 4.4 special warnings and special precautions for use).

4.3 Contraindications

Loperamide is contraindicated:

- in patients with known hypersensitivity to loperamide hydrochloride or to any of the excipients
- in children aged less than 4 years

Loperamide should not be used as the primary therapy:

- in patients with acute dysentery which is characterised by blood in stools and elevated body temperature.
- 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 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 should be discontinued promptly when ileus or constipation are present or when abdominal distension develops, especially in severely dehydrated children.

4.4 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.

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). Patients should not exceed the recommended dose and/or the recommended duration of treatment.

In patients with diarrhoea, especially in children, fluid and electrolyte depletion may occur. In such cases administration of appropriate fluid and electrolyte replacement therapy is the most important measure. Loperamide should not be given to children aged 2 to 6 years without medical prescription and supervision.

In acute diarrhoea, if clinical improvement is not observed within 48 hours, the administration of Loperamide should be discontinued and patients should be advised to consult their doctor.

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 toxic megacolon in AIDS patients with infectious colitis (viral or 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 first pass metabolism. Patients with hepatic dysfunction should be monitored closely for signs of central nervous system (CNS) toxicity.

Excipients

Contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medications on loperamide

In vitro studies have shown that loperamide is metabolised by cytochrome P450 3A4 and 2C8 enzymes and is a substrate for P-glycoprotein.

Opioid-like central nervous system effects have been reported in volunteer studies with concomitant administration of loperamide (16 mg or 24 mg single dose) with quinidine (600mg or 800mg). Quinidine may increase penetration of loperamide into the brain due to inhibition of central P-glycoprotein. The clinical significance of the pharmacokinetic interaction with P-glycoprotein inhibitors when loperamide is given at recommended dosages (2mg, up to 16mg maximum daily dose) is unknown.

Concomitant administration of loperamide 16 mg and ritonavir, an inhibitor of both P-glycoprotein and CYP3A4, resulted in a two to three-fold increase in the AUC of loperamide but without evidence of enhanced central nervous system effect.

The concomitant administration of loperamide (4mg 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 (16mg 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.

Effect of loperamide on other medications

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 Pregnancy and lactation

Although there are no indications that loperamide possesses teratogenic or embryotoxic properties, as with other drugs, it is not advisable to administer loperamide in pregnancy, especially during the first trimester.

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

Tiredness, dizziness or drowsiness may occur in the setting of diarrheal syndromes treated with Loperamide. 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. $\geq 1\%$ 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 diarrhea) or post-marketing experience.

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 |
| 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 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 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 suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Large doses of Loperamide may cause features of opioid poisoning. The following patients should be referred for medical assessment:

- All patients who have taken a deliberate overdose
- All children
- Symptomatic adults
- Adults who have ingested 0.4mg/Kg of Loperamide or more.

Adults who have accidentally ingested less than 0.4mg/Kg and who have no new symptoms since the time of ingestion should be advised to seek medical attention if symptoms develop.

The effects of overdose will be potentiated by concurrent ingestion of alcohol and/or other centrally active drugs.

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. If untreated deep coma and respiratory arrest can occur. Children, and patients with hepatic dysfunction, may be more sensitive to CNS effects.

Pin point pupils are often present but are not a reliable clinical sign. Their absence does not exclude opiate toxicity.

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.

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.

5.1 Pharmacodynamic properties

Antipropulsives, A07D A03

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.

Studies remain to be done to show the value of loperamide in acute infective diarrhoea. It should not be used to treat young children. Loperamide is also used in ileostomy management to control the volume in discharge. 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 4mg 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 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

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.

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 – 240 times the maximum human use level) loperamide impaired fertility and foetal survival in association with maternal toxicity in rats. Lower doses had no effects on maternal or foetal health and did not affect peri- and post-natal development.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose Monohydrate

Maize Starch

Magnesium Stearate

Cap

Quinoline Yellow Oxide E104

Indigo Carmine E132

Titanium Dioxide E171

Gelatin

Body

Erythrosine E127

Indigo Carmine E132

Black Iron Oxide E172

Titanium Dioxide E171

Gelatin

6.2 Incompatibilities

None known

6.3 Shelf life

48 months - blister packs

36 months - polypropylene pots

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

White, opaque PVC 250µm/hard temper aluminium foil 25µm blister packs

Polypropylene pots with white polyethylene caps with optional use of polyethylene ullage fillers

Blister packaging 4, 6, 8, 10, 12, 18, 20, 28, 30, 60, 250, 500

Polypropylene pots 4, 6, 8, 10, 12, 18, 20, 28, 50, 100, 250, 500

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No specific instructions for use/handling.

7. MARKETING AUTHORISATION HOLDER

Strides Pharma UK Ltd
Unit 4 Metro Centre
Tolpits Lane
Watford
Hertfordshire
WD18 9SS

8 MARKETING AUTHORISATION NUMBER(S)

PL 13606/0045

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

04/11/1998

10 DATE OF REVISION OF THE TEXT

01/05/2018