

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

LoModine 2mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Loperamide hydrochloride 2mg

For full list of excipients, see section 6.1

Contains lactose 100mg per capsule

3 PHARMACEUTICAL FORM

Size 4, green opaque cap and a mauve opaque body, hard gelatin capsule marked "LOMODINE 2" on the cap

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 and children aged 18 years and over following initial diagnosis by a doctor.

4.2 Posology and method of administration

The capsules should be taken with liquid.

Acute diarrhoea:

Adults and children over 12 years: two capsules (4mg) initially, followed by 1 capsule (2mg) after every loose stool. The usual dosage is 3 to 4 capsules (6mg-8mg) a day; the maximum daily dose should not exceed 6 capsules (12mg).

Symptomatic treatment of acute episodes of diarrhoea associated with Irritable Bowel Syndrome in adults and children aged 18 years and over:

Two capsules (4mg) to be taken initially, followed by 1 capsule (2mg) after every loose stool, or as previously advised by your doctor.

The maximum daily dose should not exceed 6 capsules (12mg). If symptoms persist for more than 48 hours consult your doctor.

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, 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).

Method of administration

Oral use

4.3 Contraindications

LoModine 2mg capsules are contraindicated:

- in patients with known hypersensitivity to loperamide hydrochloride or to any of the excipients
- in children aged less than 12 years
- in patients with acute dysentery which is characterised by blood in stools and elevated body temperature.
- when ileus or constipation are present or when abdominal distension develops, especially in severely dehydrated children
- 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 must be discontinued promptly when constipation, abdominal distension or ileus develop.

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 acute diarrhoea, especially in children, and in the frail and elderly 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 under 12 years without medical prescription and supervision. Use of this product 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 Loperamide should be discontinued and patients should be advised to consult their doctor.

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 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.

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

LoModine 2mg Capsules contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose- galactose malabsorption should not take this medicine.

Special Warnings to be included in the leaflet:

Only take LoModine 2mg 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

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 (16mg or 24mg 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 16mg 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.

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

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, loss of consciousness, depressed level of consciousness, 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 (See section 4.8, Undesirable effects).

4.8 Undesirable effects

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 both) 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 combined, including trials in children :≤12years (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

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 and patients with hepatic dysfunction may be more sensitive to CNS effects.

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

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

Blister packaging: 4, 6, 8, 10, 16, 18

Not all pack sizes may be marketed

6.6 Special precautions for disposal

No specific instructions for use/handling

7. MARKETING AUTHORISATION HOLDER

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Trading as: Co-pharma

8 MARKETING AUTHORISATION NUMBER(S)

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19/12/2011

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03/08/2017