

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Boots Pharmaceuticals Diarrhoea Relief 2 mg Hard Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredient

Loperamide Hydrochloride 2 mg per capsule.

Excipients: Each hard capsule contains 101.25 mg lactose monohydrate and 4.8 microgram Ponceau 4R (E124).

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Capsules, hard (capsule).

Opaque green cap printed 0611 in black ink and opaque grey body.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the symptomatic treatment of acute diarrhoea in adults and children over 12 years.

4.2 Posology and method of administration

The capsules should be taken with liquid. For oral administration.

Adults, including the elderly and children over 12 years

The initial dose is 2 capsules (4 mg) followed by 1 capsule (2 mg) after every subsequent loose stool up to a maximum of five capsules in 24 hours.

Children under 12 years

Not recommended.

If symptoms persist for more than 24 hours consult your doctor.

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

4.3 Contraindications

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

The loperamide HCl capsule should not be used in children under 12 years of age.

Loperamide HCl should not be used as the primary therapy:

- 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.

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

4.4 Special warnings and precautions for use

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

In patients with diarrhoea, especially in children, frail and elderly patients, fluid and electrolyte depletion may occur. In such cases administration of appropriate fluid and electrolyte replacement therapy is the most important measure.

In acute diarrhoea, if clinical improvement is not observed within 24 hours, the administration of loperamide HCl should be discontinued and patients should be advised to consult their physician.

This product should not be used for prolonged periods. Diarrhoea is a common presentation of a number of significant gastrointestinal conditions. This medicine should not be used for prolonged periods until an underlying cause for persistent diarrhoea has been investigated and diagnosed by a doctor.

Patients with AIDS treated with loperamide HCl 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 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.

Cardiac events including QT interval and QRS complex prolongation, torsade 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.

Keep all medicines out of the reach of children.

If symptoms persist for more than 24 hours consult your doctor.

Information related specifically to the excipients in this formulation (see Section 6.1)

Ponceau 4R (E124) can cause allergic reactions.

Lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interactions

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 P-glycoprotein 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 doses, is unknown.

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).

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

Concomitant treatment with oral desmopressin resulted in a 2-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

It is not advisable to administer this medicine in pregnancy. Women who are pregnant or breast feeding should therefore be advised to consult their doctor for appropriate treatment.

Although there is no indication that loperamide HCl possesses teratogenic or embryotoxic properties it should not be administered in pregnancy.

Small amounts of loperamide HCl may appear in human breast-milk. Therefore loperamide HCl is not recommended during breast-feeding.

4.7 Effects on ability to drive and use machines

Tiredness, dizziness or drowsiness may occur in the setting of diarrhoeal syndromes treated with loperamide HCl. 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 3076 adults and children aged ≥ 12 years who participated in 31 controlled and uncontrolled clinical trials of loperamide HCl used for the treatment of diarrhoea. Of these, 26 trials were in acute diarrhoea (N=2755) and 5 trials were in chronic diarrhoea (N=321).

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%). In clinical trials in chronic diarrhoea, the most commonly reported (i.e. $\geq 1\%$ incidence) ADRs were: flatulence (2.8%), constipation (2.2%), nausea (1.2%) and dizziness (1.2%).

Table 1 displays ADRs that have been reported with the use of loperamide HCl from either clinical trial (in acute or chronic diarrhoea or both) of post-marketing experience.

The frequency categories use the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1000$); and very rare ($< 1/10,000$).

Table 1 Adverse Drug Reactions

System Organ Class	Indication		
	Acute Diarrhoea (N=2755)	Chronic Diarrhoea (N=321)	Acute & Chronic Diarrhoea and post marketing experience

Immune System Disorders Hypersensitivity reaction ^a , Anaphylactic reaction (including Anaphylactic shock) ^a , Anaphylactoid reaction ^a			Rare
Nervous System Disorders Headache Dizziness Somnolence ^a Loss of consciousness ^a , Stupor ^a , Depressed level of consciousness ^a , Hypertonia ^a , Coordination abnormality ^a	Common Uncommon	Uncommon Common	Common Common Uncommon Rare
Eye Disorders Miosis ^a			Rare
Gastrointestinal Disorders Constipation, Nausea, Flatulence Abdominal pain, Abdominal discomfort, Dry mouth Abdominal pain upper, Vomiting Dyspepsia Ileus ^a (including paralytic ileus), Megacolon ^a (including toxic megacolon ^b), Abdominal distension Acute pancreatitis	Common Uncommon Uncommon Rare Not known	Common Uncommon Uncommon Not known	Common Uncommon Uncommon Uncommon Rare Rare Not known
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	Uncommon		Uncommon Rare
Renal and urinary disorders Urinary retention ^a			Rare
General Disorders and Administration Site Conditions Fatigue ^a			Rare

^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 for adults and children, the frequency is estimated from all clinical trials with loperamide HCl combined, including trials in children ≤12 years (N=3683).

^b: See section 4.4 Special warnings and precautions for use.

For clinical trial ADRs where no frequency is presented, the term was not observed or considered an ADR for this indication.

Paediatric population

The safety of loperamide HCl was evaluated in 607 patients aged 10 days to 13 years who participated in 13 controlled and uncontrolled clinical trials of loperamide HCl used for the treatment of acute diarrhoea. In general, the ADR profile in this patient population was similar to that seen in clinical trials of loperamide HCl in adults and children aged 12 years and over.

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 HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 OverdoseSymptoms

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

In individuals who have ingested overdoses of loperamide, cardiac events such as QT interval and QRS complex prolongation, torsade 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. Administration of activated charcoal may be recommended.

5 PHARMACOLOGICAL PROPERTIES**5.1 Pharmacodynamic properties**

Loperamide hydrochloride is a synthetic opioid which inhibits gut motility by binding to opiate receptors in the gut wall and may also reduce gastrointestinal secretions, resulting in improvement in diarrhoea symptoms. Loperamide also increases the tone of the anal sphincter.

In a double blind randomised trial in 213 patients with acute diarrhoea, loperamide (56 patients) was compared with two other common antidiarrhoeal agents and placebo. Onset of antidiarrhoeal effect occurred as soon as one hour after intake of a 4mg dose of loperamide.

5.2 Pharmacokinetic properties

More than 65% of a dose of loperamide is reported to be absorbed from the gastrointestinal tract. The drug undergoes considerable first pass metabolism in the liver and excretion via the bile in the faeces as the inactive conjugate. As a result of the drug's high affinity for the gut wall and its high first pass metabolism very little loperamide reaches the systemic circulation and therefore there is only a small amount of urinary excretion. The elimination half life is reported to be about 10 hours.

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.

6 PHARMACEUTICAL PARTICULARS**6.1 List of excipients**

Lactose monohydrate
Magnesium stearate
Maize starch (pregelatinised)

Hard gelatin capsule

Gelatin
Ponceau 4R (E124)
Indigo Carmine (E132)
Titanium dioxide (E171)
Yellow and black iron oxides (E172)

Ink
Black iron oxide (E172)
Shellac
Propylene Glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30°C.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

1. Blister of clear 250 micron PVC and 20 micron aluminium foil.
Pack size: 6, 12, 18.
2. Blister of clear 250 micron PVC coated with 40 gsm PVdC and 20 micron aluminium foil.
Pack size: 6, 12, 18.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Taw Pharma (Ireland) Ltd
104 Lower Baggot Street
Dublin 2
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8 MARKETING AUTHORISATION NUMBER

PA23081/002/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 6th December 2002
Date of last renewal: 6th December 2007

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