

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Imodium® LiquiRelief 2mg Soft Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 2 mg Loperamide hydrochloride.

Excipient with known effect – Each capsule contains 115.31 mg Propylene Glycol which is equivalent to 0.65 mg/mg, also contains trace amounts of soya lecithin.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Capsule, soft (Capsules)

A clear blue size 2, oval soft gelatin capsule

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

ACUTE DIARRHOEA

Adults and children aged 12 years and over:

2 capsules initially followed by 1 capsule after every loose stool. The capsules should be taken with water.

The maximum daily dose should not exceed 5 capsules.

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

Method of administration

Oral use.

4.3 Contraindications

Imodium LiquiRelief must not be used in:

- Children less than 12 years of age
- Patients with a known hypersensitivity (allergy) to any component of the product
- Acute dysentery, which is characterised by blood in stool and high fever
- Acute ulcerative colitis
- Pseudomembranous colitis associated with broad spectrum antibiotics
- Patients with bacterial enterocolitis caused by invasive organisms including Salmonella, Shigella and Campylobacter
- This product contains traces of soya lecithin, if you are allergic to peanut or soya, do not use this medicinal product

Imodium LiquiRelief 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. It must be discontinued promptly if constipation, subileus and/or abdominal distension develop.

4.4 Special warnings and precautions for use

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

Antimotility agents such as loperamide may precipitate ileus and toxic megacolon in patients with ulcerative colitis, or pseudomembranous colitis associated with broad-spectrum antibiotics and should be avoided in severe acute attacks. It may be used cautiously in mild or less severe attacks as an adjunct to other measures, but should be discontinued should abdominal distention or other untoward symptoms occur.

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 this medicine 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.

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

Patients with AIDS treated with this medicine 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.

In cases of acute diarrhoea, if symptoms persist for more than 24 hours, patients should be advised to consult their physician.

Consult your doctor if you develop new symptoms, or if your symptoms worsen, or your symptoms have not improved over two weeks.

Cardiac events including QT interval and QRS complex 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.

4.5 Interaction with other medicinal products and other forms of interaction

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 dosages, 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. 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

Pregnancy

Safety in human pregnancy has not been established although studies in animals have not demonstrated any teratogenic effects. As with other drugs, it is not advisable to administer this medicine in 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

The effect on human fertility has not been evaluated.

4.7 Effects on ability to drive and use machines

Tiredness, dizziness, or drowsiness may occur when diarrhoea is treated with this medicine. Therefore, it is advisable to use caution when driving a car or operating machinery. See Section 4.8, Undesirable Effects.

4.8 Undesirable effects

Adults and children aged ≥ 12 years

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 diarrhoea) 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 $< 1/1,000$); very rare ($< 1/10,000$); not known (cannot be estimated from the available data).

Table 1: Adverse Drug Reactions

System Organ Class	Indication			Not known
	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	Acute pancreatitis
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 HPRA Pharmacovigilance, website: www.hpra.ie.

4.9 Overdose

Signs and 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. 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 and QRS complex 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. Upon cessation, cases of drug withdrawal syndrome have been observed in individuals abusing, misusing, or intentionally overdosing with excessively large doses of loperamide.

Treatment:

In cases of overdose, ECG monitoring for QT interval prolongation should be initiated.

If CNS symptoms of overdose occur, naloxone may be given as an antidote. Since the duration of action of loperamide is longer than that of naloxone 1 to 3 hrs), 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 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Antipropulsives; ATC code: A07DA03

Loperamide binds to the opiate receptor in the gut wall, reducing propulsive peristalsis and increasing intestinal transit time. Loperamide increases the tone of the anal sphincter.

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.

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 data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction and development.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule fill

Propylene glycol monocaprylate

Propylene glycol (E1520)

Purified water

Capsule shell

Gelatin

Glycerol 99% (E422)

Propylene glycol (E1520)

FD&C Blue (E133)

Soya Lecithin (E322)

Triglycerides, medium chain

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C.

Store in the original package in order to protect from moisture and light.

6.5 Nature and contents of container

PVC/PVDC aluminium blister packs are packed in cardboard cartons containing 12 capsules.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

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PA 23490/025/003

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