

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Imodium 1mg/5ml Oral Solution.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml of oral solution contains 1mg loperamide hydrochloride.

Excipients: Methyl parahydroxybenzoate (E218)
Propyl parahydroxybenzoate (E216)
Alcohol

3 PHARMACEUTICAL FORM

Oral solution.

A clear, red, slightly viscous fruit-flavoured oral solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Adults

As an adjunct in the management of acute diarrhoea, together with appropriate fluid and electrolyte replacement.

In the symptomatic control of diarrhoea associated with chronic inflammatory bowel disease, eg., Crohn's disease and ulcerative colitis, as an adjunct to specific measures such as corticosteroids and sulphasalazine. Use in these conditions should be under specialist supervision.

In the adjunctive short-term, control of post-surgical diarrhoea, including ileostomy.

Children

For the occasional use in the control of intractable diarrhoea under specialist supervision.

Since persistent diarrhoea can be an indicator of potentially serious conditions, the underlying cause must always be investigated.

4.2 Posology and method of administration

Method of Administration

Oral use.

- a. As an adjunct in the management of acute diarrhoea

Adults and children 9-12 years

2 to 4mg (10 to 20ml) is the usual initial dose, followed by 2mg (10ml) three times daily. The maximum daily dose should not exceed 10mg.

Children 4-8 years

A total maximum daily dose of 4mg (20ml) in divided doses.

Children under 4 years

Not recommended.

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

b. For the Symptomatic Treatment of Diarrhoea Associated with Chronic Bowel DisordersAdults only

Studies have shown that patients may need differing amounts of loperamide. The starting dosage should be between 4 to 8mg (20 to 40ml) per day in divided doses, depending on severity. If required, this dose can be adjusted according to response. Having established the patient's daily maintenance dose, the solution may be administered on a twice daily regimen.

4.3 Contraindications

- Imodium is contraindicated in patients under 4 years of age
- Imodium is contraindicated in patients with a known hypersensitivity to loperamide hydrochloride or to any of the excipients
- Imodium should not be used as the primary therapy:
 - In patients with acute dysentery, which is characterised by blood in the 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.
- Imodium should not be used when the inhibition of peristalsis is to be avoided due to the possible risk of significant sequelae including ileus, megacolon and toxic megacolon. Imodium 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 etiology can be determined, specific treatment should be given when appropriate.

The necessity for specific therapy, such as anti-infectives, should be borne in mind, particularly should treatment be required for a period longer than three days.

Loperamide should be used with caution when hepatic function, necessary for the drug's metabolism, is defective as this may result in relative overdose leading to CNS toxicity.

Patients with AIDS treated with Imodium 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.

Antimotility agents such as loperamide may precipitate ileus and toxic megacolon in patients with ulcerative colitis, 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 promptly should abdominal distension or other untoward symptoms occur.

The stated dose should not be exceeded.

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

The safety of Imodium in human pregnancy has not been established. Small amounts of loperamide may appear in human breast milk. Therefore, Imodium 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 when diarrhoea is treated with Imodium. 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

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 $< 1/1,000$); 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.

4.9 Overdose

Overdose (relative or absolute) may lead to constipation, urinary retention, ileus and central nervous system depression (miosis, muscular hypertonia, somnolence and bradypnoea). Naloxone may be given as an antidote, repeated as necessary over an observation period of at least 48 hours.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Antipropulsives; ATC code: A07DA03

Loperamide binds to the opiate receptors in the gut wall, reducing propulsive peristalsis, increasing intestinal transit time and enhancing resorption of water and electrolytes.

5.2 Pharmacokinetic properties

Loperamide is well absorbed from the gut, but is almost completely extracted and metabolised by the liver where it is conjugated and excreted via the bile. Due to this very high first pass effect, plasma concentration of unchanged drug remains low. The half life of loperamide in man is 10.8 hours with a range of 9-14 hours. Excretion occurs mainly through the faeces.

5.3 Preclinical safety data

No relevant information additional to that contained elsewhere in the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol
Sodium Saccharin
Methyl parahydroxybenzoate (E218)
Propyl parahydroxybenzoate (E216)
Cochineal Red A (E124)
Raspberry flavour
Redcurrant flavour
Ethanol
Citric acid monohydrate
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Amber glass bottle with either an aluminium cap coated on the inside with PVC or child-resistant polypropylene screw cap lined inside with an LDPE insert, in an outer cardboard carton.

A 5ml natural polypropylene (food-grade) dosing cup is also provided, graduated for 2.5ml and 5ml.

Each bottle contains 100 ml of solution.

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

McNeil Healthcare (Ireland) Ltd.
Airton Road
Tallaght
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 823/56/4

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 June 1976

Date of last renewal: 30 January 2009

10 DATE OF REVISION OF THE TEXT

February 2012