Imodium 1 mg/5 ml oral solution

Summary of Product Characteristics Updated 26-Jan-2016 | Janssen-Cilag Ltd

1. Name of the medicinal product

Imodium 1 mg/5 ml oral solution

2. Qualitative and quantitative composition

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

Excipients with known effect:

Each 5 ml of oral solution contains

0.365 mg of Ethanol

3.6 mg of Methyl parahydroxybenzoate (E218)

0.4 mg of Propyl parahydroxybenzoate (E216)

0. 5 mg Cochineal Red A (E124)

4.85 mg Sodium

For the full list of excipients, see section 6.1

3. Pharmaceutical form

Oral solution for oral administration.

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

4. Clinical particulars

4.1 Therapeutic indications

For the symptomatic treatment of acute diarrhoea of any aetiology including acute exacerbations of chronic diarrhoea for periods of up to 5 days in adults and children over 4 years. For the symptomatic treatment of chronic diarrhoea in adults.

4.2 Posology and method of administration

Acute diarrhoea

Adults:	Four 5 ml doses initially, followed by two 5 ml doses after each loose stool. The total daily dose should not exceed sixteen 5 ml doses.
Children:	The following doses should not be exceeded.
Children over 8 years:	Two 5 ml doses four times daily with the duration limited to 5 days.
Children 4 - 8 years:	One 5 ml dose three or four times daily with the duration limited to 3 days.

Not recommended for children under 4 years of age.

There is limited data available regarding use in children below 12 years of age. Please refer to Section 4.8 Undesirable effects.

Further investigation into the cause of the diarrhoea should be considered if there is no improvement within two days of starting treatment with Imodium.

Chronic diarrhoea

Adults:	Patients may need widely differing amounts of Imodium. The starting dose should be between four and eight 5 ml doses per day in divided doses, depending on severity. If required this dose can be adjusted up to a maximum of sixteen 5 ml doses daily. Having established the patient's daily maintenance dose, Imodium may be administered on a twice daily regimen. Tolerance has not been observed and therefore subsequent dosage adjustment should be unnecessary.

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 warnings and special precautions for use).

Method of Administration: Oral use.

4.3 Contraindications

Imodium is contraindicated in:

• patients with a known hypersensitivity to loperamide hydrochloride or to any of the excipients.

• children less than 4 years of age.

• when inhibition of peristalsis is to be avoided due to the possible risk of significant sequelae including ileus, megacolon and toxic megacolon, in particular:

-when ileus, constipation or abdominal distension develop,

- 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 alone in acute dysentery, which is characterised by blood in stools and elevated body temperatures.

4.4 Special warnings and precautions for use

In patients with diarrhoea, especially young children, fluid and electrolyte depletion may occur. Use of Imodium does not preclude the administration of appropriate fluid and electrolyte replacement therapy.

Treatment of diarrhoea with Imodium is only symptomatic.

Since persistent diarrhoea can be an indicator of potentially more serious conditions, Imodium should not be used for prolonged periods of time and the underlying cause of the diarrhoea should be investigated if clinical improvement is not observed within 48 hours of initiating treatment. Whenever an underlying etiology can be determined, specific treatment should be given when appropriate.

Although no pharmacokinetic data are available in patients with hepatic impairment, Imodium must be used with caution in these patients because of reduced first pass metabolism (eg in cases of severe hepatic disturbance), as this might result in a relative overdose leading to CNS toxicity.

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

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.

Imodium oral solution contains:

• sodium saccharin (4.85 mg of sodium per 5 ml dose): To be taken into consideration by patients on a controlled sodium diet

• methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216): these may cause an allergic reaction (possibly delayed)

• cochineal red A (E124): may cause allergic reactions

• small amounts of ethanol (alcohol), less than 100 mg per dose

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 (2 mg, up to 16 mg maximum daily dose), 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.

The concomitant administration of loperamide with oral desmopressin may result 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 which accelerate gastrointestinal transit may decrease its effect.

4.6 Fertility, pregnancy and lactation

Safety in human pregnancy has not been established although studies in animals have not demonstrated any teratogenic effects or embryotoxic properties. As with other drugs, it is not advisable to administer Imodium in pregnancy, especially during the first trimester.

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

Women who are breast feeding infants should therefore be advised to consult their doctor for appropriate treatment.

4.7 Effects on ability to drive and use machines

Loss of consciousness, depressed level of consciousness, 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

The safety of loperamide hydrochloride was evaluated in 3076 adults and children aged ≥12 years who participated in 31 controlled and uncontrolled clinical trials of loperamide hydrochloride 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. ≥1% incidence) adverse reactions in clinical trials with loperamide hydrochloride 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. ≥1% incidence) adverse reactions were: flatulence (2.8%), constipation (2.2%), nausea (1.2%) and dizziness (1.2%).

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

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

Table 1: Adverse Reactions

System Organ Class and Frequency	**Adverse Reaction**
Immune System Disorders	
Rare	Hypersensitivity reaction, Anaphylactic reaction (including Anaphylactic shock), Anaphylactoid reaction
Nervous System Disorders	
Common	Headache, Dizziness
Uncommon	Somnolence
Rare	Loss of consciousness, Stupor, Depressed level of consciousness, Hypertonia, Coordination abnormality
Eye Disorders	
Rare	Miosis
Gastrointestinal Disorders	
Common	Constipation, Nausea, Flatulence
Uncommon	Abdominal pain, Abdominal discomfort, Dry mouth, Abdominal pain upper, Vomiting, Dyspepsia
Rare	Ileus (including paralytic ileus), Megacolon (including toxic megacolon – see section 4.4), Abdominal distension

Skin and Subcutaneous Tissue Disorders	
Uncommon	Rash
Rare	Bullous eruption (including Stevens-Johnson syndrome, Toxic epidermal necrolysis and Erythema multiforme), Angioedema, Urticaria, Pruritus
Renal and Urinary Disorders	
Rare	Urinary retention
General Disorders and Administration Site Conditions	
Rare	Fatigue

A number of the adverse reactions reported during the clinical investigations and post-marketing experience with loperamide hydrochloride are frequent symptoms of the underlying diarrhoeal syndrome (for example abdominal pain/discomfort, nausea, vomiting, dry mouth, tiredness, drowsiness, dizziness, constipation, and flatulence). These symptoms are often difficult to distinguish from undesirable drug effects.

Paediatric population

The safety of loperamide hydrochloride was evaluated in 607 patients aged 10 days to 13 years, who participated in 13 controlled and uncontrolled clinical trials of loperamide hydrochloride used for the treatment of acute diarrhoea. In general, the adverse reactions profile in this patient population was similar to that seen in clinical trials of loperamide hydrochloride 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 the Yellow Card Scheme at: www.yellowcard.mhra.gov.uk.

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), constipation, urinary retention and ileus may occur. Children and patients with hepatic dysfunction may be more sensitive to CNS effects than adults.

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. 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.

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 metabolised, 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.

Paediatric Population: No pharmacokinetic studies were performed in the paediatric population. It is expected that pharmacokinetic behaviour of loperamide and drug-drug interactions with loperamide will be similar to those in adults.

5.3 Preclinical safety data

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 (40mg/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

Glycerol

Sodium saccharin

Methyl parahydroxybenzoate (E218)

Propyl parahydroxybenzoate (E216)

Cochineal Red A (E124)

Raspberry Flavour

Redcurrant Flavour

Ethanol (96%)

Citric acid monohydrate

Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

60 months.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Amber glass bottle with either a pilfer-proof aluminium screw cap coated on the inside with PVC or a child resistant polypropylene screw cap lined inside with an LDPE insert and a 5 ml or 10 ml polypropylene measuring cup.

Imodium oral solution may be presented in bottle sizes of 30, 40, 50, 90 and 100 mls.

(Not all pack sizes may be marketed.)

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing authorisation holder

Janssen-Cilag Ltd.

50-100 Holmers Farm Way

High Wycombe

Buckinghamshire

HP12 4EG

UK

8. Marketing authorisation number(s)

PL 00242/0040

9. Date of first authorisation/renewal of the authorisation

Date of first authorisation: 03 December 1975

Date of renewal of authorisation: 10 March 2005

10. Date of revision of the text

25th January 2016

Company Contact Details

Janssen-Cilag Ltd
http://www.janssen-cilag.co.uk

Address
50 - 100 Holmers Farm Way, High Wycombe, Bucks, HP12 4EG

Fax
+44 (0)1494 567 568

Medical Information Direct Line
+44 (0)800 731 8450

Customer Care direct line
+44 (0)800 731 5550

Telephone
+44 (0)1494 567 567

Medical Information Website
http://www.janssen-medinfo.co.uk

Medical Information e-mail
medinfo@janssen-cilag.co.uk

Medical Information Fax
+44 (0) 1494 567 445