เอกสารกำกับยาสำหรับแพทย์ฉบับภาษาอังกฤษ

1. Name of the Medicinal Product

1.1 Product Name

IMODIUM® (loperamide hydrochloride) INN: loperamide hydrochloride

1.2 Strength

2 mg loperamide hydrochloride (HCl) per capsule
For excipients, see *List of Excipients*.

1.3 Pharmaceutical Dosage Form

Capsule, hard

2. Qualitative and Quantitative Composition

White powder filled in capsules (size 4) with green cap and dark grey body
2 mg loperamide hydrochloride (HCl) per capsule
For excipients, see *List of Excipients*.

3. Pharmaceutical Form

Capsule, hard

4. Clinical Particulars

4.1 Therapeutic indication

IMODIUM is indicated for

1. The symptomatic control of acute and chronic diarrhea
2. Reducing the number and volume of stools and to harden their consistency in patients with an ileostomy

MOPH Warnings

1. Do not use in children and elder.
2. In acute diarrhea, if clinical improvement is not observed within 48 hours, the administration of this product should be discontinued and consult the physician.

4.2 Posology and method of administration

Dosage
Adults
Capsules
Acute diarrhea
The initial dose is 2 capsules (4 mg) for adults; followed by 1 capsule (2 mg) after every subsequent loose stool.

Chronic diarrhea
The initial dose is 2 capsules (4 mg) daily for adults; this initial dose should be adjusted until 1-2 solid stools a day are obtained, which is usually achieved with a maintenance dose of 1-6 capsules (2 mg-12 mg) daily.

The maximum dose for acute and chronic diarrhea is 8 capsules (16 mg) daily for adults.

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 *Warnings and Precautions*).

Administration
Capsules
The capsules should be taken with liquid

4.3 Contraindication
Loperamide HCl is contraindicated in patients with a known hypersensitivity to loperamide HCl or to any of the excipients.
Loperamide HCl is contraindicated in children under 12 years of age and elderly patients.
Loperamide HCl should not be used as the primary therapy:

- in patients with acute dysentery, which is characterized 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 warning and precautions
Treatment of diarrhea with loperamide HCl is only symptomatic. Whenever an underlying etiology can be determined, specific treatment should be given when appropriate.

Do not use Loperamide HCl in children without physician consultation, fluid and electrolyte depletion may occur, administration of appropriate fluid and electrolyte replacement therapy is the most important measure.

In acute diarrhea, if clinical improvement is not observed within 48 hours, the administration of loperamide HCl should be discontinued and patients should be advised to consult their physician.

Patients with AIDS treated with loperamide HCl for diarrhea 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. Patients with hepatic dysfunction should be monitored closely for signs of central nervous system (CNS) toxicity.

Abuse and misuse of loperamide, as an opioid substitute, have been described in individuals with opioid addiction (see *Overdose*).

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 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 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

Although there are no indications that loperamide HCl possesses teratogenic or embryotoxic properties, the anticipated therapeutic benefits should be weighed against potential hazards before loperamide HCl is given during pregnancy, especially during the first trimester.

Breast-feeding

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

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.

4.7 Effect on ability to drive and use machine

Tiredness, dizziness, or drowsiness may occur in the setting of diarrheal syndromes treated with loperamide HCl. Therefore, it is advisable to use caution when driving a car or operating machinery.

4.8 Undesirable effects

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of loperamide HCl based on the comprehensive assessment of the available adverse event information. A causal relationship with loperamide HCl cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Clinical trial data

Adults and pediatrics (12 years and over)

Acute diarrhea

The safety of loperamide HCl was evaluated in 2755 patients aged ≥12 years who participated in 26 controlled and uncontrolled clinical trials of loperamide HCl used for the treatment of acute diarrhea. Adverse reactions reported for ≥1% of loperamide HCl-treated patients are shown in Table 1.

Table 1. Adverse Reactions Reported by ≥1% of Loperamide HCl-treated Patients in 26 Clinical Trials of Loperamide HCl in Acute Diarrhea

System Organ Class Adverse Reaction	**Loperamide HCl % (N=2755)**
Nervous System Disorders	
Headache	1.2
Gastrointestinal Disorders	
Constipation	2.7
Flatulence	1.7
Nausea	1.1

Adverse reactions reported by <1% of loperamide HCl-treated patients (N=2755) in the above clinical trial dataset are shown in Table 2.

Table 2. Adverse Reactions Reported by <1% of Loperamide HCl-treated Patients in 26 Clinical Trials of Loperamide HCl in Acute Diarrhea

System Organ Class Adverse Reaction
Nervous System Disorders
Dizziness
Gastrointestinal Disorders
Dry mouth
Abdominal pain
Vomiting
Abdominal discomfort
Abdominal pain upper
Abdominal distension
Skin and Subcutaneous Tissue Disorders
Rash

Chronic diarrhea

The safety of loperamide HCl was evaluated in 321 patients who participated in 5 controlled and uncontrolled clinical trials of loperamide HCl used for the treatment of chronic diarrhea. Treatment periods ranged from 1 week to 52 months.

Table 3. Adverse Reactions Reported by ≥1% of Loperamide HCl-treated Patients in 5 Clinical Trials of Loperamide HCl in Chronic Diarrhea

System Organ Class Adverse Reaction	**Loperamide HCl % (N=321)**
Nervous System Disorders	
Dizziness	1.2
Gastrointestinal Disorders	
Flatulence	2.8
Constipation	2.2
Nausea	1.2

Adverse reactions reported by <1% of loperamide HCl-treated patients (N=321) in the above clinical trial dataset are shown in Table 4.

Table 4. Adverse Reactions Reported by <1% of Loperamide HCl-treated Patients in 5 Clinical Trials of Loperamide HCl in Chronic Diarrhea

System Organ Class Adverse Reaction
Nervous System Disorders
Headache
Gastrointestinal Disorders
Abdominal pain
Dry mouth
Abdominal discomfort
Dyspepsia

Pediatrics (under 12 years)

Acute diarrhea

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 diarrhea. Adverse reactions reported for ≥1% of loperamide HCl-treated patients are shown in Table 5.

Table 5. Adverse Reactions Reported by ≥1% of Loperamide HCl-treated Patients <12 Years in 13 Clinical Trials of Loperamide HCl in Acute Diarrhea

System Organ Class Adverse Reaction	**Loperamide HCl** **%** **(N=607)**
Gastrointestinal Disorders	
Vomiting	1.2

Adverse reactions reported by <1% of loperamide HCl-treated patients <12 years (N=607) in the above clinical trial dataset are shown in Table 6.

Table 6. Adverse Reactions Reported by <1% of Loperamide HCl-treated Patients <12 Years in 13 Clinical Trials of Loperamide HCl in Acute Diarrhea

System Organ Class Adverse Reaction
Nervous System Disorders
Somnolence
Dizziness
Headache
Gastrointestinal Disorders
Nausea
Abdominal pain
Constipation
Skin and Subcutaneous Tissue Disorders
Rash

Postmarketing data

Adverse reactions first identified during postmarketing experience with loperamide HCl are included in Tables 7. In table, the frequencies are provided according to the following convention:

Very common	≥ 1/10
Common	≥ 1/100 and < 1/10
Uncommon	≥ 1/1000 and < 1/100

Rare	≥ 1/10000 and < 1/1000
Very rare	< 1/10000, including isolated reports

In Tables 7, adverse reactions are presented by frequency category based on spontaneous reporting rates.

Table 7. Adverse Reactions Identified During Postmarketing Experience with Loperamide HCl by Frequency Category Estimated from Spontaneous Reporting Rates in Adults and Pediatrics

Immune System Disorders	
Very rare	Hypersensitivity reaction, Anaphylactic reaction (including Anaphylactic shock) and Anaphylactoid reaction
Nervous System Disorders	
Very rare	Coordination abnormality, Depressed level of consciousness, Hypertonia, Loss of consciousness, Somnolence, Stupor
Eye Disorders	
Very rare	Miosis
Gastrointestinal Disorders	
Very rare	Ileus (including paralytic ileus), Megacolon (including toxic megacolon[a]), Glossodynia[b]
Skin and Subcutaneous Tissue Disorders	
Very rare	Angioedema, Bullous eruption (including Stevens-Johnson syndrome, Toxic epidermal necrolysis and Erythema multiforme), Pruritus, Urticaria
Renal and Urinary Disorders	
Very rare	Urinary retention
General Disorders and Administration Site Conditions	
Very rare	Fatigue

a: See *Warnings and Precautions*
b: Reported for the orodispersible tablet only

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), urinary retention and ileus may occur. Children may be more sensitive to CNS effects than adults.

In individuals who have intentionally ingested overdoses (reported in doses from 40 mg up to 792 mg per day) of loperamide HCl, QT interval and QRS complex prolongation and/or serious ventricular arrhythmias, including Torsade de Pointes, have been observed (see *Warnings and Precautions*). Fatal cases have also been reported. Abuse, misuse and/or overdose with excessively large doses of loperamide, may unmask Brugada syndrome.

Treatment

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

If CNS 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.
Because strategies for the management of overdose are continually evolving, it is advisable to contact a poison control center (where available) to determine the latest recommendations for the management of an overdose.

5. Pharmacological Properties

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Antipropulsives, ATC code: A07 DA03

Mechanism of action

Loperamide binds to opiate receptors in the gut wall. Consequently, it inhibits the release of acetylcholine and prostaglandins, thereby reducing propulsive peristalsis, and increasing intestinal transit time. Loperamide increases the tone of the anal sphincter, thereby reducing incontinence and urgency.

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%. Loperamide HCl formulations (hard and soft capsule, coated and uncoated tablet, chewable and orodispersible tablet, oral solution) are bioequivalent in terms of rate and extent of loperamide absorption.

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.

Excretion

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 feces.

Special populations

Pediatrics

No pharmacokinetic studies were performed in the pediatric population. It is expected that pharmacokinetic behavior of loperamide and drug-drug interactions with loperamide will be similar to those in adults

5.3 Preclinical Safety Data

Chronic repeat dose toxicity studies on loperamide of up to 12 months in the dog and 18 months in the rat have not shown any toxic effect other than some reduction in body weight or body weight gain and food consumption at daily doses of up to 5 mg/kg/day {8 times the Maximum Human Use Level (MHUL, 16 mg/50 kg/day)} and 40 mg/kg/day (20 times MHUL) respectively, based on body surface area dose comparisons (mg/m^2). The No Observed Adverse Effect Levels (NOAEL) in these studies were 0.3 mg/kg/day (~0.5 times MHUL) and 2.5 mg/kg/day (~1.3 times MHUL) in dogs and rats respectively.

Within its therapeutically relevant concentration range and at significant multiples of this range (up to 47-fold), loperamide has no significant cardiac electrophysiological effects. However, at extremely high concentrations associated with intentional overdose (see *Warnings and Precautions*), loperamide has cardiac electrophysiological actions consisting of inhibition of potassium (hERG) and sodium currents, and arrhythmias in *in vitro* and *in vivo* animal models.

Carcinogenicity and Mutagenicity

There was no carcinogenic potential. Results of *in vivo* and *in vitro* studies carried out indicated that loperamide is not genotoxic.

Reproductive Toxicology

In reproduction studies where pregnant rats were dosed during pregnancy and/or lactation, very high doses of loperamide (40 mg/kg/day-20 times MHUL) resulted in maternal toxicity, impaired fertility and reduced fetal/pup survival. Lower NOAEL doses (≥10 mg/kg – 5 times MHUL) revealed no effects on maternal or fetal health and did not affect peri- and post-natal development.

6. Pharmaceutical Particulars

6.1 List of excipients

Capsules

Lactose monohydrate
Magnesium stearate
Maize starch
Talc

6.2 Incompatibilities

None known.

6.3 Shelf life

See expiry date on the outer pack.

6.4 Special precautions for storage

Store below 30° C.

Keep out of the sight and reach of children.

6.5 Nature and contents of container

1 carton contains 1 blister. Each blister contains 6 capsules.

7. Marketing Authorization Holder

Janssen-Cilag Ltd.
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8. Marketing Authorization Numbers

1C XX/XX

9. Date of authorization

DDMMMYYYY

10. Date of revision of the text

17 September 2018

Manufactured by

Lusomedicamenta Sociedade Técnica Farmacêutica, S.A., Barcarena, Portugal

Imported by

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