DESCRIPTION

Imodium® contains the synthetic antidiarrhoeal for oral use, Loperamide HCl. Imodium® is available in capsules. Each capsule contains 2mg Loperamide HCl.

PHARMACEUTICAL FORM

White powder filled in capsules with green cap and dark grey body

PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: A07 DA03
Antipropulsives

Loperamide binds to the opiate receptor 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.

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 orodispersable 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 faeces.

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

INDICATION

Loperamide HCl is indicated for the symptomatic control of acute and chronic diarrhea. In patients with an ileostomy it can be used to reduce the number and volume of stools and to harden their consistency.

DOSAGE AND ADMINISTRATION

Adults and Pediatrics 6 to 17 Years

Capsules

The capsules should be taken with liquid.

Acute diarrhea: the initial dose is 2 capsules (4 mg) for adults and 1 capsule (2 mg) for children; followed by 1 capsule (2 mg) after every subsequent loose stool.

Chronic diarrhea: the initial dose is 2 capsules (4 mg) daily for adults and 1 capsule (2 mg) daily for children; 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; in children it must be related to the body weight (3 capsules/20 kg) but should not exceed a maximum of 8 capsules per day.

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 Warnings and Precautions)*.

CONTRAINDICATIONS

- Loperamide HCl is contraindicated in patients with a known hypersensitivity to Loperamide HCl or to any of the excipients.
- Loperamide HCl should not be used in children under 6 years of age.
- 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.

WARNINGS 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.

In patients with diarrhea, especially in children, fluid and electrolyte depletion may occur. In such cases 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. This medicine must be used with caution in patients with hepatic impairment as it may result in a relative overdose leading to CNS toxicity.

Warning: Loperamide is not recommended for children under 6 years of age. Its use has been associated with fatal episodes of paralytic ileus in infants and young children.
The use of higher than the recommended doses for control of the diarrhea may lead to abnormal heart rhythms and serious cardiac events leading to death. Cases of syncope and ventricular tachycardia have been reported in adult patients receiving the recommended dosage of IMODIUM®. Some of these patients were taking other drugs or had other risk factors that may have increased their risk of cardiac adverse reactions.

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

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 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.

PREGNANCY AND LACTATION

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.

Small amount 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.

EFFECTS OF DRIVING ABILITY AND USE OF MACHINERY

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.

ADVERSE REACTIONS

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 Paediatrics 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

Paediatrics Under 12 Years

Acute Diarrhea

The safety of Loperamide HCl was evaluated in 607 patients aged less than 12 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

Post-marketing Experience

Adverse reactions first identified during post-marketing experience with Loperamide HCl are included in Table 7. In each 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
Not known	cannot be estimated from the available data

In Table 7, ADRs are presented by frequency category based on spontaneous reporting rates.

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

Cardiac Disorders	
Not known	QT/QTc interval prolongation, Torsades de Pointes, other ventricular arrhythmias, cardiac arrest, syncope, and death[a]
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]
Not known	Acute pancreatitis
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 section
b: Reported for the orodispersible tablet only

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), 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, prolongation of the QT/QTc interval, Torsades de Pointes, other ventricular arrhythmias and cardiac arrest, 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.

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 case 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 HCl 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.

HOW SUPPLIED
Imodium capsules are supplied in blister 6s and in a box of 240s.

SHELF LIFE
See expiry date on the outer pack.

STORAGE CONDITIONS
Store below 30°C

NAME AND ADDRESS OF MANUFACTURER
JNTL Consumer Health (France) SAS
Domaine de Maigremont
27100 Val de Reuil
France

PRODUCT REGISTRATION HOLDER
JNTL (MALAYSIA) SDN. BHD.
Lot 3 & 5 Jalan Tandang,
46050 Petaling Jaya,
Selangor, Malaysia.

KEEP OUT OF THE SIGHT AND REACH OF CHILDREN/ JAUHI DARI KANAK-KANAK

The source of gelatin capsule is bovine

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