Imodium™

NAME OF THE MEDICINAL PRODUCT
IMODIUM

QUALITATIVE AND QUANTITATIVE COMPOSITION
2 mg loperamide hydrochloride per capsule.

PHARMACEUTICAL FORM
Capsules
White powder filled in capsules (size 4) with green cap and dark grey body.

CLINICAL PARTICULARS
Therapeutic Indications
IMODIUM 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.

Posology and Method of Administration
Adults and children 5 years and over:
- Acute diarrhea: the initial dose is 2 capsules (4mg) 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 will 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 bodyweight (3 capsules/20 kg).

Children under 2 Years
The use of IMODIUM in children under 2 years is not recommended.
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 Special warnings and special precautions for use).

Contraindications
- IMODIUM is contraindicated in patients with a known hypersensitivity to loperamide hydrochloride or to any of the excipients.
- IMODIUM is not recommended in infants below 24 months of age.
- IMODIUM should not be used as the primary therapy:
  - o in patients with acute dysentery, which is characterized by blood in stools and high fever,
  - o in patients with acute ulcerative colitis,
  - o in patients with bacterial enterocolitis caused by invasive organisms including *Salmonella*, *Shigella*, and *Campylobacter*,
  - o in patients with pseudomembranous colitis associated with the use of broad-spectrum antibiotics.

In general, IMODIUM 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. IMODIUM must be discontinued promptly when constipation, abdominal distension or ileus develop.
Treatment of diarrhea with IMODIUM is only symptomatic. Whenever an underlying etiology can be determined, specific treatment should be given when appropriate (or when indicated).

Special warnings and special precautions for use
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. IMODIUM should not be given to children under 6 years of age without medical prescription and supervision.
In acute diarrhea, if clinical improvement is not observed within 48 hours, the administration of IMODIUM should be discontinued and patients should be advised to consult their physician.
Patients with AIDS treated with IMODIUM for diarrhea 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.
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**.** Patients with hepatic dysfunction should be monitored closely for signs of CNS toxicity.
Since the majority of the drug is metabolized, and metabolites or the unchanged drug is excreted in the feces, dose adjustments in patients with a kidney disorder are not required.

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.

Pregnancy and Lactation
Although there are no indications that loperamide hydrochloride possesses teratogenic or embryotoxic properties, the anticipated therapeutic benefits should be weighed against potential hazards before IMODIUM is given during pregnancy, especially during the first trimester.
Small amounts of loperamide may appear in human breast milk. Therefore, IMODIUM is not recommended during breast-feeding.

Effects on Ability to Drive and Use Machines
Tiredness, dizziness, or drowsiness may occur in the setting of diarrheal syndromes treated with IMODIUM. Therefore, it is advisable to use caution when driving a car or operating machinery. (See section Undesirable effects.)

Undesirable Effects
Clinical trial data
The adverse events reported are summarized irrespective of the causality assessment of the investigators.
1.*) Adverse events in patients with acute diarrhea*
The adverse events with an incidence of 1.0% or greater, which were reported at least as often in patients on loperamide hydrochloride as on placebo, are presented in the table below.

	Acute Diarrhea	
	Loperamide Hydrochloride	Placebo
No. of treated patients	231	236
Gastrointestinal disorders Constipation	2.6%	0.8%

The adverse events with an incidence of 1.0% or greater, which were more frequently reported in patients on placebo than on loperamide hydrochloride, were: dry mouth, flatulence, abdominal cramp and colic.
2.) *Adverse events in patients with chronic diarrhea*
The adverse events with an incidence of 1.0% or greater, which were reported at least as often in patients on loperamide hydrochloride as on placebo, are presented in the table below.

	Chronic Diarrhea	
	Loperamide Hydrochloride	Placebo
No. of treated patients	285	277
Gastrointestinal disorders Constipation	5.3%	0.0%
Nervous system disorders Dizziness	1.4%	0.7%

The adverse events with an incidence of 1.0% or greater, which were more frequently reported in patients on placebo than on loperamide hydrochloride were: nausea, vomiting, headache, meteorism, abdominal pain, abdominal cramp and colic.
3.*) Adverse events from seventy-six controlled and uncontrolled studies in patients with acute or chronic diarrhea*
The adverse events with an incidence of 1.0% or greater in patients from all studies are given in the table below.

	Acute Diarrhea	Chronic Diarrhea	All Studies[a]
No. of treated patients	1913	1371	3740
Gastrointestinal disorders Nausea Constipation Abdominal cramps	 0.7% 1.6% 0.5%	 3.2% 1.9% 3.0%	 1.8% 1.7% 1.4%

a. All patients in all studies, including those in which it was not specified if the adverse events occurred in patients with acute or chronic diarrhea.

Post-marketing experience
The following spontaneous adverse experiences have been reported, and within each system organ class, are ranked by frequency, using the following convention:
Very common (>1/10)
Common (>1/100, < 1/10)
Uncommon (> 1/1000, < 1/100)
Rare (>1/10000, < 1/1000)
Very rare (<1/10000), including isolated reports
The frequency provided is a reflection of reporting rates for spontaneous adverse experiences and does not represent true incidence or frequency as seen with clinical trials or epidemiologic studies.
Skin and subcutaneous system disorders
Very rare: rash, urticaria and pruritus.
Isolated occurrences of angioedema, and bullous eruptions including Stevens-Johnson Syndrome, erythema multiforme, and toxic epidermal necrolysis have been reported with use of loperamide hydrochloride.
Immune system disorders
Isolated occurrences of allergic reactions and in some cases severe hypersensitivity reactions including anaphylactic shock and anaphylactoid reactions have been reported with the use of loperamide hydrochloride.
Gastrointestinal Disorders
Very rare: abdominal pain, ileus, abdominal distension, nausea, constipation, vomiting, megacolon including toxic megacolon (See Special warnings and special precautions for use), flatulence, and dyspepsia.
Renal and urinary disorders
Isolated reports of urinary retention.
Psychiatric system disorders
Very rare: drowsiness
Nervous System disorders
Very rare: Loss of consciousness, depressed level of consciousness, dizziness
A number of the adverse events reported during the clinical investigations and post marketing experience with loperamide are frequent symptoms of the underlying diarrheal syndrome (abdominal pain/discomfort, nausea, vomiting, dry mouth, tiredness, drowsiness, dizziness, constipation, and flatulence). These symptoms are often difficult to distinguish from undesirable drug effects.

Overdose
Symptoms
In case of overdose (including relative overdose due to hepatic dysfunction), central nervous system depression (stupor, coordination abnormality, somnolence, miosis, muscular hypertonia, respiratory depression), urinary retention and ileus may occur. Children may be more sensitive to CNS effects than adults.
Treatment
If symptoms of overdosage occur, naloxone can be given as an antidote. Since the duration of action of IMODIUM 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.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Pharmacotherapeutic group: ATC code: A07 DA53
Antipropulsives
Loperamide binds to the opiate receptor in the gut wall. Consequently, it inhibits the release of acetylcholine and prostaglandins, thereby reducing propulsive peristalsis, increasing intestinal transit time. Loperamide increases the tone of the anal sphincter, thereby reducing incontinence and urgency.
Due to its high affinity for the gut wall and its high first-pass metabolism, IMODIUM hardly reaches the systemic circulation.

Pharmacokinetic Properties
Loperamide is easily absorbed from the gut, but it is almost completely extracted by the liver, where it is metabolised, conjugated and excreted via the bile.
The half-life of loperamide in man is about 11 hours with a range of 9-14 hours. 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. Elimination mainly occurs by oxidative N-demethylation, which is the main metabolic pathway of loperamide. Excretion of the unchanged loperamide and the metabolites mainly occurs through the feces.

Pre-clinical Safety Data
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 gain and food consumption at daily doses of up to 5mg/kg/day {30 times the Maximum Human Use Level (MHUL)} and 40mg/kg/day (240 times MHUL) respectively. The No Toxic Effect Levels (NTEL) in these studies were 1.25mg/kg/day (8 times MHUL) and 10mg/kg/day (60 times MHUL) in dogs and rats respectively. Results of *in vivo* and *in vitro* studies carried out indicated that loperamide is not genotoxic. There was no carcinogenic potential. In reproduction studies, very high doses of loperamide (40 mg/kg/day-240 times MHUL) impaired fertility and fetal survival in association with maternal toxicity in rats. Lower doses had no effects on maternal or fetal health and did not affect peri- and post-natal development. Pre-clinical effects were observed only at exposures considered sufficiently in excess of the maximum human exposure, indicating little relevance to clinical use.

PHARMACEUTICAL PARTICULARS
List of Excipients
Lactose, maize starch, talc, magnesium stearate.
The capsule itself contains titanium dioxide, yellow ferric oxide, indigotindisulphonate sodium, gelatin, black ferrous oxide, erythrosine sodium.

Shelf Life
Observe expiry date on the outer pack.

Special Precautions for Storage
Store between 15 and 30°C.
Keep out of reach of children.

Nature and Contents of Container
IMODIUM capsules are supplied in blister packs.

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JANSSEN-CILAG

Manufactured by: see outer pack
for Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse, Belgium