PACKAGE INSERT

SCHEDULING STATUS

Schedule 2

PROPRIETARY NAME AND DOSAGE FORM

IMODIUM® CAPS capsules

COMPOSITION

Each capsule contains 2 mg loperamide hydrochloride.

The other ingredients are:

Lactose monohydrate, magnesium stearate, maize starch and talc. The capsule itself is made from yellow ferric oxide, indigotindisulphonate sodium, black ferrous oxide, erythrosine sodium, titanium dioxide and gelatine.

Contains sugar (lactose).

PHARMACOLOGICAL CLASSIFICATION

A.11.9 Medicines acting on gastro-intestinal tract. Anti-diarrhoeals

PHARMACOLOGICAL ACTION

Pharmacodynamic Properties

Loperamide hydrochloride inhibits hypermotility by direct action on the bowel wall. Its inhibition of peristalsis is the result of decreasing the activity of both the longitudinal muscles (preparatory and reflex phases) and the circular muscles (reflex phase). Loperamide hydrochloride normalises the stool in both acute and chronic diarrhoea.

Pharmacokinetic Properties

Loperamide hydrochloride is incompletely absorbed from the gut, and it is almost completely metabolised in the liver where it is conjugated and excreted via the bile.

Loperamide hydrochloride is mainly eliminated via the faeces.

INDICATIONS

Adults and children 6 years and older

- for the control and symptomatic relief of acute and chronic non-specific diarrhoea,
- inhibition of peristalsis and slowing intestinal transit time in patients with ileostomies, colostomies and other intestinal resections.

CONTRAINDICATIONS

- patients with a known hypersensitivity to loperamide hydrochloride or to any of the excipients.
- infants below 24 months of age.

- IMODIUM CAPS should not be used as the primary therapy:
    - in patients with acute dysentery, which is characterised by blood in stools and high fever,
    - patients with acute ulcerative colitis,
    - patients with bacterial enterocolitis caused by invasive organisms including Salmonella, Shigella, and Campylobacter,
    - patients with pseudomembranous colitis associated with the use of broad-spectrum antibiotics,
    - Ileus irrespective of cause.

WARNINGS and SPECIAL PRECAUTIONS

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

Treatment of diarrhoea with IMODIUM CAPS is only symptomatic. Whenever an underlying aetiology can be determined, specific treatment should be given when appropriate (or when indicated).

In patients with diarrhoea, especially in **children**, fluid and electrolyte depletion may occur. In such cases administration of appropriate fluid and electrolyte replacement (oral rehydration therapy [ORT]) is the most important measure. IMODIUM CAPS should not be given to children less than 6 years of age. IMODIUM CAPS are not recommended for use in acute or chronic diarrhoea in children under the age of 6 years.

HIV-infected patients treated with IMODIUM CAPS for diarrhoea should have therapy stopped at the earliest signs of abdominal distension. There have been reports of toxic megacolon in HIV-infected patients with infectious colitis from both viral and bacterial pathogens treated with IMODIUM CAPS.

Although no pharmacokinetic data are available in patients with hepatic impairment, IMODIUM CAPS should be used with caution in such patients because of reduced first pass metabolism, as it may result in relative overdose leading to central nervous system toxicity.

Cardiac events including QT interval and QRS complex prolongation and torsade de pointes have been reported in association with overdose. Some cases had a fatal outcome (see KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT). Patients should not exceed the recommended dose and/or the recommended duration of treatment.

Abuse and misuse of IMODIUM CAPS, as an opioid substitute, have been described in individuals with opioid addiction. (See KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT).

Lactose intolerance and lactase deficiency

IMODIUM CAPS contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Effects on ability to drive and use machines:

Since IMODIUM CAPS can cause dizziness, patients must take special precaution when using IMODIUM CAPS before driving or operating machinery.

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 IMODIUM CAPS (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.

The concomitant administration of IMODIUM CAPS (16 mg single dose) and ketoconazole, an inhibitor of CYP3A4 and P-glycoprotein, resulted in a 5-fold increase in loperamide plasma concentrations.

Concomitant treatment with oral desmopressin resulted in a 3-fold increase of desmopressin plasma concentrations, presumable due to slower gastrointestinal motility.

It is expected that medicines with similar pharmacological properties may potentiate loperamide's effect and that medicines that accelerate gastrointestinal transit may decrease its effects.

HUMAN REPRODUCTION

The safety of use during pregnancy and lactation has not been established. **IMODIUM CAPS** should not be used during pregnancy.

Small amounts of loperamide may appear in human breast milk. Therefore, IMODIUM CAPS should not be used by mothers breastfeeding their infant.

DOSAGE AND DIRECTIONS FOR USE

IMODIUM CAPS are not suited for children under 6 years of age.

IMODIUM CAPS should be taken with liquid.

Acute non specific diarrhoea

For adults and children of 6 years and older: 2 capsules (4 mg) for adults or 1 capsule (2 mg) for children as an initial dose, followed by 1 capsule (2 mg) after each subsequent loose stool.

Do not exceed the following maximum daily dosages:

WEIGHT IN KILOGRAMS (kg)	MAXIMUM DAILY DOSE
from 27 kg	4 capsules (8 mg)
from 34 kg	5 capsules (10 mg**)**
from 40 kg	6 capsules (12 mg)
from 47 kg	7 capsules (14 mg)
from 54 kg	8 capsules (16 mg)

IMODIUM CAPS should be stopped as soon as diarrhoea is under control.

In acute diarrhoea, if clinical improvement is not observed within 48 hours, the administration of IMODIUM CAPS should be discontinued and patients should be advised to consult their doctor.

Chronic nonspecific diarrhoea

The initial dose is 2 capsules (4 mg) daily for adults and 1 capsule (2 mg) daily for children of 6 years and over.

The initial dose should be adjusted until 1 - 2 solid stools per day are obtained. This is usually achieved on a maintenance dose of 1 - 6 capsules (2 mg – 12 mg) daily. If constipation occurs, the dosage should be decreased.

The maximum dose for acute and chronic diarrhoea is 8 capsules (16 mg) daily for adults; in children it must be related to body weight (3 capsules/20 kg).

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 CAPS should be used with caution in such patients because of reduced first pass metabolism. (see WARNINGS AND SPECIAL PRECAUTIONS).

SIDE EFFECTS

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonable associated with the use of IMODIUM CAPS based on the comprehensive assessment of the available adverse event information. A causal relationship with IMODIUM CAPS 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 medicine cannot be directly compared to rates in the clinical trials of another medicine and may not reflect the rates observed in clinical practice.

Adults and children aged ≥ 12 years

The safety of loperamide HCl was evaluated in 2 755 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. ≥ 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 (≥ 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 Drug Reactions

System Organ Class	**Indication**		
	Common	**Uncommon**	**Rare**
Nervous System Disorders	Headache	Dizziness	
Gastrointestinal Disorders	Constipation, nausea, flatulence	Abdominal pain, abdominal discomfort, dry mouth, abdominal pain upper, vomiting	Abdominal distension
Skin and Subcutaneous		Rash	

Tissue Disorders			

The table above does not differentiate between chronic and acute indications in adults and children, the frequency is estimated from all clinical trials with loperamide HCl (acute and chronic), including trials in children ≤ 12 years (N=3 683).

Table 2: Adverse drug reactions identified during post-marketing experience with loperamide HCl in adults and children

Immune system disorders Hypersensitivity reaction, anaphylactic reaction (including anaphylactic shock) and anaphylactoid reaction
Nervous system disorders Coordination abnormality, depressed level of consciousness, hypertonia, loss of consciousness, somnolence, stupor
Eye disorders Miosis
Gastrointestinal disorders Ileus (including paralytic ileus), megacolon (including toxic megacolon)
Skin and subcutaneous tissue disorders Angioedema, bullous eruption (including Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme), pruritis, urticaria
Renal and urinary disorders Urinary retention
General disorders and administration site conditions Fatigue

See section WARNINGS and SPECIAL PRECAUTIONS

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

In case of overdose (including relative overdose due to hepatic dysfunction), central nervous system depression (e.g. stupor, coordination abnormality, somnolence, miosis, muscular hypertonia and respiratory depression), urinary retention, constipation and paralytic ileus may occur. Children may be more sensitive to central nervous system effects of loperamide than adults. Convulsions have been reported in children under the age of 2 years.

Excessive inhibition of peristalsis with nausea and dryness of the mouth.

In individuals who have intentionally ingested overdoses (reported in doses from 40 mg up to 792 mg per day) of IMODIUM CAPS, QT interval and QRS complex prolongation and/or serious ventricular dysrhythmias, including Torsade de Pointes, have been observed (See WARNINGS and SPECIAL PRECAUTIONS). Fatal cases have also been reported.

Abuse, misuse and/or overdose with excessively large doses of IMODIUM, may unmask Brugada syndrome.

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

Treatment is symptomatic and supportive. Naloxone can be given as an antidote. Since the duration of action of IMODIUM CAPS 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 central nervous system depression.

IDENTIFICATION

White powder filled into hard capsules with opaque green cap and opaque dark grey body.

PRESENTATION

Cartons containing one or more blister packs of 6 capsules each.

STORAGE INSTRUCTIONS

Store at or below 25 ºC. Protect from light.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

U/11.9/213

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