PRODUCT INFORMATION- IMODIUM CAPSULES & ZAPID

1 NAME OF THE MEDICINE

Loperamide hydrochloride

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

IMODIUM Capsules contain Loperamide hydrochloride 2mg

Excipients with known effect- lactose

IMODIUM Capsules contain the inactive ingredients: maize starch, purified talc and magnesium stearate, iron oxide yellow CI77492, indigo carmine CI173015, titanium dioxide, erythrosine CI45430, iron oxide black CI177499, gelatin and water.

IMODIUM Zapid Tablets containing loperamide hydrochloride 2 mg and contain the inactive ingredients gelatin, mannitol, aspartame, sodium bicarbonate and mint flavour.

3 PHARMACEUTICAL FORM

IMODIUM Capsules are supplied in a gelatin capsule with a light grey body and dark green cap.

IMODIUM Zapid is a white to off- white circular freeze dried tablet.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

IMODIUM is indicated for:

- The control and symptomatic treatment of acute nonspecific diarrhoea, and of chronic diarrhoea.
- Reducing the volume of discharge in patients with ileostomies, colostomies, and other intestinal resections.

4.2 DOSE AND METHOD OF ADMINISTRATION

IMODIUM capsule is administered orally with the aid of liquid.

IMODIUM Zapid tablet should be placed on the tongue. The tablet will dissolve and should be swallowed with saliva. No liquid intake is necessary

Acute Diarrhoea

The recommended initial dose of IMODIUM in adults is two capsules or tablets (4 mg) followed by one capsule or tablet (2 mg) after each unformed stool. Daily dose should not exceed eight capsules or tablets (16 mg). Clinical improvement is usually observed within 48 hours.

Chronic Diarrhoea and Reduction in Volume of Discharge of Intestinal Resections

The recommended initial dose of IMODIUM is two capsules or tablets (4 mg) followed by one capsule or tablet (2 mg) after each unformed stool until diarrhoea is controlled, after which dosage of IMODIUM should be reduced to meet individual requirements. When the optimal maintenance daily dosage has thus been established, this amount can then be administered as a single dose or in two or three divided doses.

The average daily maintenance dosage in clinical trials was two to four capsules (4-8 mg). A dosage of five capsules (10 mg) was rarely exceeded. A temporary exacerbation of diarrhoea was controlled by increasing the Ioperamide dosage to achieve further control followed by titration back to the established maintenance dose.

4.3 CONTRAINDICATIONS

- Hypersensitivity to any ingredients
- In patients with acute dysentery, which is characterised by blood in stools and high fever;
- In patients with acute ulcerative colitis or Crohn's disease;
- 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.
- In children under the age of 12 years

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 diarrhoea with IMODIUM is only symptomatic. Whenever an underlying aetiology can be determined, specific treatment should be given when appropriate.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Fluid and electrolyte depletion may occur in patients who have diarrhoea. The use of IMODIUM does not preclude the administration of appropriate fluid and electrolyte therapy.

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

Anticholinergic Effects In vitro studies have demonstrated anti-cholinergic properties. Hence, caution should be used in patients with glaucoma, urinary bladder neck obstruction, pyloric obstruction, significant gastric retention, or intestinal stasis..

Use in patients with AIDS

Use with caution in patients with AIDS. 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 obstipation with an increased risk for toxic megacolon in AIDS patients with infectious colitis from both viral and bacterial pathogens treated with loperamide hydrochloride.

Renal impairment

Since the majority of the drug is metabolised, and the metabolites or the unchanged drug is excreted in the faeces, dose adjustments in patients with a kidney disorder are not required.

Use in hepatic impairment

IMODIUM must be used with caution in patients with hepatic insufficiency as it may result in a relative overdose leading to CNS toxicity. Abuse and misuse of loperamide, as an opioid substitute, have been described in individuals with opioid addiction (see Overdose)

Use in the elderly

No data available

Paediatric use

IMODIUM is contraindicated in children under the age of 12 years.

Effects on laboratory tests

No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Although the pharmacological effect of Loperamide hydrochloride is not associated with a central action, patients with concomitant administration of tranquillisers or alcohol should be carefully observed.

Other drugs that affect loperamide hydrochloride theoretical interactions

Consideration should always be given with new drugs as to possible interaction with monoamine oxidase inhibitors. Theoretically, the combination of IMODIUM with monoamine oxidase inhibitors (which are also inhibitors of liver microsomal enzymes) may potentiate the action of Ioperamide by blocking its metabolic pathway.

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 2-3 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.

4.6 FERTILITY, PREGNANCY AND LACTATION

USE IN PREGNANCY – PREGNANCY CATEGORY B3

Safe use of IMODIUM during pregnancy has not been established. Reproduction studies performed in rats and rabbits with high doses did not demonstrate evidence of impaired fertility or harm to the offspring due to Ioperamide hydrochloride. Higher doses impaired maternal and neonate survival, but even higher doses did not demonstrate teratogenicity. Such experience cannot exclude the possibility of damage to the foetus. IMODIUM should be used in only if the potential benefit justifies the risk to the foetus. Therefore, pregnant woman should be advised to consult their doctor for appropriate treatment.

Use in lactation

There is little information on the excretion of IMODIUM in human milk, but as small amounts of the drug are detectable in the milk of nursing mothers, the use of IMODIUM is not recommended in breast feeding subjects. Woman who are breastfeeding should be advised to consult their doctor for appropriate treatment. In a peri- and postnatal study, Ioperamide administered to female rats at dosage of 40mg/kg indicated a possible adverse effect of lactation as evidenced in a decreased pup-survival rate.

Effects on fertility

No data available

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The adverse effects reported during clinical investigations of IMODIUM are difficult to distinguish from symptoms associated with the diarrhoeal syndrome. Adverse experiences recorded during clinical studies with IMODIUM were generally of a minor and self-limiting nature. They were more commonly observed during treatment of chronic diarrhoea.

Acute diarrhea (12 years and over)

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

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

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
Dry mouth
Abdominal pain
Dyspepsia
Abdominal discomfort

Post Marketing Data

Adverse drug reactions (ADRs) identified during Post-marketing experience with Imodium are included in the following table. The frequencies are provided according to the following convention:

Very common	≥1/10
Common	≥1/100 and < 1/10
Uncommon	≥1/1,000 and <1/100
Rare	≥1/10,000 and <1/1,000
Very rare	<1/10,000

Not known (cannot be estimated from the available data)

Skin and subcutaneous tissue 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 Ioperamide hydrochloride.

Immune system disorders

Very rare- Isolated occurrences of allergic reactions and in some cases severe hypersensitivity reactions including anaphylactic shock and anaphylactoid reactions have been reported with use of Ioperamide hydrochloride.

Gastrointestinal disorders

Very rare – abdominal pain, ileus, abdominal distension, nausea, constipation, vomiting, megacolon including toxic megacolon, flatulence, glossodynia[1] and dyspepsia (see **Contraindications** and **Precautions**).

Renal and urinary disorders

Very rare- Isolated reports of urinary retention.

Psychiatric system disorders

Very rare: drowsiness.

Nervous system disorders

Very rare: Loss of consciousness, depressed level of consciousness, dizziness, coordination abnormality, hypertonia, somnolence

Eye disorders

Very rare: Miosis

General Disorders and Administration site conditions

Very rare: Fatigue

Special senses

Very rare: taste disturbance

A number of the adverse events reported during the clinical investigations and post-marketing experience with loperamide are frequent symptoms of the underlying diarrhoeal 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.

With IMODIUM Zapid some subjects have complained about a burning or prickling sensation on the tongue immediately following its use.

1. Reported for orodispersible tablet only

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at: https://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Symptoms

In case of overdose (including relative overdose due to hepatic dysfunction), central nervous system depression (stupor, co-ordination abnormality, somnolence, miosis, muscular hypertonia, respiratory depression), urinary retention and paralytic ileus may occur. Children may be more sensitive to CNS effects than adults.

In clinical trials using loperamide hydrochloride, an adult took three 20mg doses within a 24-hour period, was nauseated after the second dose, and vomited after the third dose.

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. Upon cessation, cases of drug withdrawal syndrome, have been observed in individuals abusing, misusing or intentionally overdosing with excessively large doses of loperamide.

Treatment

If vomiting has occurred spontaneously, a slurry of 100 g of activated charcoal should be administered orally as soon as fluids can be maintained.

If vomiting has not occurred, gastric lavage should be performed, followed by administration of 100 g of activated charcoal slurry through gastric tube. In the case of overdosage, patient should be monitored for signs of CNS depression and/or respiratory depression for at least 24 hours. If CNS depression is observed, naloxone may be administered. If responsive to naloxone, vital signs must be monitored carefully for recurrence of symptoms of drug overdosage for at least 24 hours after the last dose of naloxone. In view of the prolonged action of Ioperamide and the short duration (one to three hours) of naloxone, the patient must be monitored closely and treated repeatedly with naloxone as indicated. Based on the fact that relatively little Ioperamide is excreted in urine, forced diuresis is not expected to be effective for IMODIUM overdosage.

Physical dependence to IMODIUM in humans has not been observed. However, studies in monkeys demonstrated that Ioperamide hydrochloride at high dose produced symptoms of physical dependence of the morphine type

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group- antipropulsive

Mechanism of action

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. Studies suggest that loperamide may increase the tone of the anal sphincter, reducing incontinence and urgency.

Due to its high affinity for the gut wall and its high first-pass metabolism, loperamide hardly reaches the systemic circulation. In man, as a constipating agent, loperamide on a mg to mg basis is about 3 times more potent than diphenoxylate hydrochloride and 25 times more potent than codeine phosphate.

The onset of action, as determined in clinical studies with volunteers, indicated that clinical improvement occurs within 1-3 hours following drug administration (4 mg dose). The duration of action was determined from the interval between the time treatment was stopped due to constipation and the time bowel motion and stool consistency were again normal. In normal test subjects, a single 4 mg dose of Ioperamide significantly increased the median time of defaecation from 23 hours to 41 hours.

In those patients where biochemical and haematological parameters were monitored during clinical trials, no trends toward abnormality during Ioperamide therapy were noted. Similarly, urinalysis, ECG, and clinical ophthalmological examinations did not show trends towards abnormality.

CNS Activity

Animal studies indicate that Ioperamide is devoid of analgesic properties (2-16 mg/kg). Studies in morphine-dependent monkeys demonstrated that loperamide hydrochloride in high S.C. doses prevented signs of morphine withdrawal. However, in humans the naloxone challenge pupil test which when positive indicated opiate-like effects, was negative when performed after a single high dose or after more than two years of therapeutic use (mean dose 4 mg/day) of Ioperamide hydrochloride.

Cardiovascular Effects

In human volunteers, analysis of electrocardiograms obtained pre-therapy, and then two and six hours after administration of Ioperamide hydrochloride (16 mg), revealed no evidence of cardiovascular toxicity.

5.2 PHARMACOKINETIC PROPERTIES

Metabolism

The absorption, excretion and tissue distribution of a single oral dose of 3H-labelled Ioperamide was studied in rats (1.25 mg/kg) and man (2 mg). In man, peak plasma levels of about 2 ng/ml of intact drug occurred at 4 hours.

In the rat, approximately 15% of the administered dose was recovered after 96 hours. The highest residual concentration was found in the liver; the lowest in fatty tissue. About 60% of the administered dose was recovered from the faeces mainly as unchanged drug. Urinary excretion accounted for approximately 5% of which only 20% was unmetabolised Ioperamide. The existence of an enterohepatic shunt has been shown in rats and is assumed in man.

Excretion

The half-life of loperamide in man is about 11 hours with a range of 9-14 hours. 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 faeces. The combined cumulative urinary excretion of Ioperamide and its conjugates accounts for only about 2% of the administered dose

Bioavailability

In a formal study IMODIUM Capsules and Caplets were not considered to be bioequivalent. As the antidiarrhoeal action of Ioperamide is considered to be due to a local effect, the clinical significance is unknown but is probably not significant.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available

Carcinogenicity

No data available

PHARMACEUTICAL PARTICULARS

5.4 LIST OF EXCIPIENTS

Refer to Section 2 - Qualitative and quantitative composition

5.5 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine. Refer to section 4.5: Interactions with other medicines and other forms of interactions.

5.6 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

5.7 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

5.8 NATURE AND CONTENTS OF CONTAINER

IMODIUM Capsules are available in cartons containing 8 and 20capsules in a blister pack.

IMODIUM Zapid tablets are available in cartons containing 6 and 12 tablets in a blister pack.

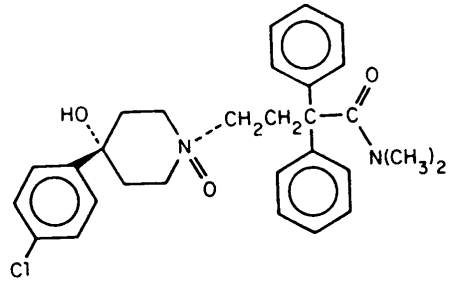
5.9 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

5.10 PHYSICOCHEMICAL PROPERTIES

Loperamide hydrochloride is 4-(4-chlorophenyl)-4-hydroxy-N, N-dimethyl-a, a-diphenyl-1-piperidinebutyramide monohydrochloride, a synthetic compound for oral use. It is a white to yellowish, amorphous or microcrystalline powder, insoluble in water.

Chemical structure



Chemical Name: C29H33CIN202. HCI; 513.49

CAS number 34552-83-5

6 MEDICINE SCHEDULE (POISONS STANDARD)

Pharmacy Medicine (S2)

7 SPONSOR

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8 DATE OF FIRST APPROVAL

August 1991

9 DATE OF REVISION

November 30 2021

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Reformatting of PI
4.4, 4.6, 4.8, 4.9	Additional safety information