
IMODIUM[®] Capsules & Caplets

IMODIUM[®] Zapid

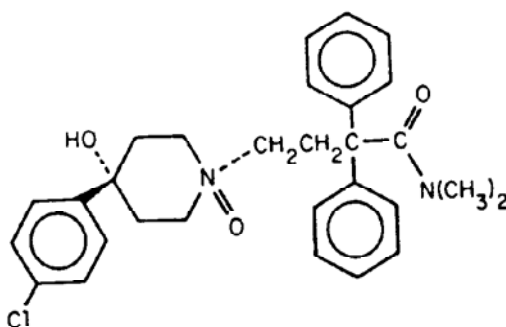
DATA SHEET

NAME OF THE DRUG

Loperamide hydrochloride

DESCRIPTION

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



CAS: 34552-83-5

$C_{29}H_{33}ClN_2O_2 \cdot HCl$

Mol wt. 513.49

IMODIUM Capsules contain loperamide hydrochloride 2mg in a No. 4 gelatin capsule with a light grey body and dark green cap. IMODIUM Capsules contain the inactive ingredients lactose, 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 Caplets contain loperamide hydrochloride 2mg is a light green, capsule-shaped, uncoated tablet embossed with IMODIUM A-D on one side, scored on the other side and embossed with 2 MG.

IMODIUM Caplets contain the inactive ingredients microcrystalline cellulose, calcium phosphate, magnesium stearate, colloidal silica anhydrous, quinoline yellow CI147005 and brilliant blue FCF CI42090.

IMODIUM Zapid Tablets contain loperamide hydrochloride 2 mg, is a white to off-white circular freeze dried tablet. IMODIUM Zapid contains the inactive ingredients gelatin, mannitol, aspartame, sodium bicarbonate and mint flavour.

PHARMACOLOGY

Pharmacological classification - antidiarrhoeal.

Pharmacodynamics

Antidiarrhoeal Activity: 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 loperamide 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 loperamide therapy were noted. Similarly, urinalysis, ECG, and clinical ophthalmological examinations did not show trends towards abnormality.

CNS Activity: Animal studies indicate that loperamide 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 loperamide hydrochloride.

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

Pharmacokinetics

Metabolism and Excretion

The absorption, excretion and tissue distribution of a single oral dose of ³H-labelled loperamide 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 loperamide. The existence of an enterohepatic shunt has been shown in rats and is assumed in man.

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 loperamide 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 loperamide is considered to be due to a local effect, the clinical significance is unknown but is probably not significant.

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.

CONTRAINDICATIONS

IMODIUM is contraindicated in patients with known hypersensitivity to loperamide or to any of the excipients (see **Description**).

IMODIUM should not be used as the primary therapy:

- in patients with acute dysentery, which is characterised 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.

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 etiology can be determined, specific treatment should be given when appropriate.

Use in Children

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

PRECAUTIONS

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.

Use in 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 loperamide 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 pregnant women only if the potential benefit justifies the risk to the foetus.

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. In a peri- and postnatal study, loperamide administered to female rats at dosage of 40mg/kg indicated a possible adverse effect of lactation as evidenced in a decreased pup-survival rate.

Use in Children

(See contraindications).

Abuse and Dependence

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

Use in patients with hepatic impairment

IMODIUM should be used with caution in patients with hepatic insufficiency because of reduced first pass metabolism. Patients with hepatic dysfunction should be monitored closely for signs of central nervous system (CNS) toxicity.

Use in patients with 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 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 toxic megacolon in AIDS patients with infectious colitis from both viral and bacterial pathogens treated with loperamide hydrochloride.

Effects on ability to drive and use machinery

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.

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.

Interactions with other drugs

Effect of loperamide hydrochloride on other drugs

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 loperamide 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.

ADVERSE REACTIONS

Clinical trial data

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.

Adverse events reported from 76 controlled and uncontrolled studies in patients with acute or chronic diarrhoea, irrespective of the causality assessment of the investigators, are summarised in the Table 1.

Table 1: Adverse events with an incidence of 1.0% or greater in patients from all studies

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

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

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 (>1/1,000, < 1/100); rare (>1/10,000, <1/1,000); very rare (>1/10,000), 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 epidemiological studies.

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 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 use of loperamide hydrochloride.

Gastrointestinal disorders

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

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 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.

DOSAGE AND ADMINISTRATION

IMODIUM capsule and caplet is administered orally with the aid of liquid.

IMODIUM Zapid tablets should be placed on the tongue. The tablet will dissolve and should be swallowed with saliva. No liquid intake is necessary. Do not halve the tablet.

Caution

IMODIUM capsules, IMODIUM caplets and IMODIUM Zapid tablets are contraindicated in children under the age of 12 years.

Acute Diarrhoea

The recommended initial dose of IMODIUM in adults is two capsules or caplets or tablets (4 mg) followed by one capsule or caplet or tablet (2 mg) after each unformed stool. Daily dose should not exceed eight capsules or caplets 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 caplets or tablets (4 mg) followed by one capsule or caplet 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 loperamide dosage to achieve further control followed by titration back to the established maintenance dose.

OVERDOSAGE

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, and vomited after the third dose.

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 loperamide 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 loperamide is excreted in urine, forced diuresis is not expected to be effective for IMODIUM overdosage.

Contact the Poisons Information Centre in Australia on 13 11 26 or in New Zealand on 0800 POISON or 0800 764 766 for the latest advice on the treatment of oral poisoning.

MEDICINES CLASSIFICATION

IMODIUM Capsules - Prescription Medicine

IMODIUM Caplets and IMODIUM Zapid – Pharmacy-Only Medicine

PRESENTATION AND STORAGE

IMODIUM Capsules are available in cartons containing 60 capsules in a blister pack. Store below 30°C.

IMODIUM Caplets are available in cartons containing 8 and 20 tablets in a blister pack. Store below 30°C.

IMODIUM Zapid tablets are available in cartons containing 12 tablets in a blister pack. Store below 25°C. Store in the original package.

SPONSOR

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