Immodium / loprarmide

IMODIUM (loperamide hydrochloride) is indicated for the control and symptomatic relief of acute nonspecific diarrhea and of chronic diarrhea associated with inflammatory bowel disease. Imodium is also indicated for reducing the volume of discharge from ileostomies.

(1 capsule = 2 mg)

Patients should receive appropriate fluid and electrolyte replacement as needed.

Acute Diarrhea

Adults: The recommended initial dose is 4mg (two capsules) followed by 2 mg (one capsule) after each unformed stool. Daily dose should not exceed 16mg (eight capsules). Clinical improvement is usually observed within 48 hours.

Children: In children 2 to 5 years of age (20 kg or less), the non-prescription liquid formulation immodium 1 mg/5 mL should be used; for ages 6 to 12, either immodium Capsules or Liquid may be used. For children 2 to 12 years of age, the following schedule for capsules or liquid will usually fulfill initial dosage requirements:

Recommended First Day Dosage Schedule

Two to five years: 1 mg t.i.d. (3mg daily dose) (13 to 20 kg) Six to eight years: 2 mg b.i.d. (4mg daily dose) (20 to 30 kg) Eight to twelve years: 2mg t.i.d. (6mg daily dose) (greater than 30 kg)

Recommended Subsequent Daily Dosage

Following the first treatment day, it is recommended that subsequent Immodium doses (1 mg/10 kg body weight) be administered only after a loose stool. Total daily dosage should not exceed recommended dosages for the first day.

Chronic Diarrhea

Children: Although Immodium has been studied in a limited number of children with chronic diarrhea; the therapeutic dose for

the treatment of chronic diarrhea in a pediatric population has not been established.

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

The average daily maintenance dosage in clinical trials was 4 to 8 mg (two to four capsules). A dosage of 16 mg (eight capsules) was rarely exceeded. If clinical improvement is not observed after treatment with 16 mg per day for at least 10 days, symptoms are unlikely to be controlled by further administration. Immodium administration may be continued if diarrhea cannot be adequately controlled with diet or specific treatment.

Children under 2 Years

The use of Immodium in children under 2 years is not recommended. There have been rare reports of paralytic ileus associated with abdominal distention. Most of these reports occurred in the setting of acute dysentery, overdose, and with very young children less than two years of age.

Elderly

No formal pharmacokinetic studies were conducted in elderly subjects. However, there were no major differences reported in the drug disposition in elderly patients with diarrhea relative to young patients. No dosage adjustment is required for the elderly.

Renal Impairment

No pharmacokinetic data are available in patients with renal impairment. Since the metabolites and the unchanged drug are mainly excreted in the feces, no dosage adjustment is required for patients with renal impairment.

Hepatic Impairment

Although no pharmacokinetic data are available in patients with hepatic impairment, Immodium should be used with caution in such patients because of reduced first pass metabolism.

Skin and subcutaneous tissue disorders

Rash, pruritus, urticaria, angioedema, and extremely rare cases of bullous eruption including erythema multiforme, Stevens-Johnson syndrome and Toxic Epidermal Necrolysis have been reported with use of Immodium.

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 Immodium.

Gastrointestinal disorders

Dry mouth, abdominal pain, distention or discomfort, nausea, vomiting, flatulence, dyspepsia, constipation, paralytic ileus, megacolon, including toxic megacolon.

Renal and urinary disorders

Urinary retention

Nervous system disorders

Drowsiness, dizziness

General disorders and administrative site conditions

Tiredness

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.

Drug Abuse And Dependence

Abuse

A specific clinical study designed to assess the abuse potential of loperamide at high doses resulted in a finding of extremely low abuse potential.

Dependence

Studies in morphine-dependent monkeys demonstrated that loperamide hydrochloride at doses above those recommended for humans prevented signs of morphine withdrawal. However, in humans, the naloxone challenge pupil test, which when positive indicates opiate-like effects, performed after a single high dose, or after more than two years of therapeutic use of Imodium was negative. Orally administered Imodium formulated with magnesium stearate is both highly insoluble and penetrates the CNS poorly.

DRUG INTERACTIONS

Nonclinical data have shown that loperamide is a P-glycoprotein substrate. Concomitant administration of loperamide (16 mg single dose) with a 600 mg single dose of either quinidine, or ritonavir, both of which are P-glycoprotein inhibitors, resulted in a 2- to 3- fold increase in loperamide plasma levels. Due to the potential for enhanced central effects when loperamide is coadministered with quinidine and with ritonavir, caution should be exercised when loperamide is administered at the recommended dosages (2 mg, up to 16 mg maximum daily dose) with P-glycoprotein inhibitors.

When a single 16-mg dose of loperamide is coadministered with a 600 mg single dose of saquinavir, loperamide decreased saquinavir exposure by 54%, which may be of clinical relevance due to reduction of therapeutic efficacy of saquinavir. The effect of saquinavir on loperamide is of less clinical significance. Therefore, when loperamide is given with saquinavir, the therapeutic efficacy of saquinavir should be closely monitored.

WARNINGS

Fluid and electrolyte depletion often occur in patients who have diarrhea. In such cases, administration of appropriate fluid and electrolytes is very important. The use of Imodium does not preclude the need for appropriate fluid and electrolyte therapy.

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 distention 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.

Patients with AIDS treated with Imodium for diarrhea should have therapy stopped at the earliest signs of abdominal distention. There have been isolated reports of toxic megacolon in AIDS patients with infectious colitis from both viral and bacterial pathogens treated with loperamide hydrochloride. Imodium should be used with special caution in young children because of the greater variability of response in this age group. Dehydration, particularly in younger children, may further influence the variability of response to Imodium.

PRECAUTIONS

General

Extremely rare allergic reactions including anaphylaxis and anaphylactic shock have been reported. In acute diarrhea, 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. 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. No pharmacokinetic data are available in patients with renal impairment. Since it has been reported

that the majority of the drug is metabolized and metabolites or the unchanged drug is excreted mainly in the feces, dosage adjustments in patients with renal impairment are not required. No formal studies have been conducted to evaluate the pharmacokinetics of loperamide in elderly subjects. However, in two studies that enrolled elderly patients, there were no major differences in the drug disposition in elderly patients with diarrhea relative to young patients.

Carcinogenesis, mutagenesis, impairment of fertility

In an 18-month rat study with oral doses up to 40 mg/kg/day (21 times the maximum human dose of 16 mg/day, based on a body surface area comparison), there was no evidence of carcinogenesis.

Loperamide was not genotoxic in the Ames test, the SOS chromotest in *E. coli*, the dominant lethal test in female mice, or the mouse embryo cell transformation assay.

Fertility and reproductive performance was evaluated in rats using oral doses of 2.5, 10, and 40 mg/kg/day in one study, and 1, 5, 10, 20, and 40 mg/kg/day (females only) in a second study. Oral administration of 20 mg/kg/day (approximately 11 times the human dose based on a body surface area comparison) and higher produced strong impairment of female fertility. Treatment of female rats with up to 10 mg/kg/day p.o. (approximately 5 times the human dose based on a body surface area comparison) had no effect on fertility. Treatment of male rats with 40 mg/kg/day p.o. (approximately 21 times the human dose based on a body surface area comparison) produced impairment of male fertility, whereas administration of up to 10 mg/kg/day (approximately 5 times the human dose based on a body surface area comparison) had no effect.

Pregnancy

Teratogenic Effects Pregnancy Category C

Teratology studies have been performed in rats using oral doses of 2.5, 10, and 40 mg/kg/day, and in rabbits using oral doses of 5, 20, and 40 mg/kg/day. These studies have revealed no evidence of impaired fertility or harm to the fetus at doses up to 10 mg/kg/day in

rats (5 times the human dose based on body surface area comparison) and 40 mg/kg/day in rabbits (43 times the human dose based on body surface area comparison). Treatment of rats with 40 mg/kg/day p.o. (21 times the human dose based on a body surface area comparison) produced marked impairment of fertility. The studies produced no evidence of teratogenic activity. There are no adequate and well-controlled studies in pregnant women. Loperamide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Non-teratogenic Effects

In a peri- and post-natal reproduction study in rats, oral administration of 40 mg/kg/day produced impairment of growth and survival of offspring.

Nursing Mothers

Small amounts of loperamide may appear in human breast milk. Therefore, Imodium is not recommended during breast-feeding.

Pediatric Use

See the "**WARNINGS**" Section for information on the greater variability of response in this age group.

In case of accidental overdosage of Imodium by children, see **"OVERDOSAGE"** Section for suggested treatment.

Contraindications

Treatment should be avoided in the presence of fever or if the stool is bloody. Treatment is not recommended for patients who could suffer detrimental effects from rebound constipation. If there is a suspicion of diarrhea associated with organisms that can penetrate the intestinal walls, such as E. coli O157:H7 or salmonella, loperamide is contraindicated.

Crossing the blood-brain barrier

When loperamide is taken by itself, it cannot readily cross the blood-brain barrier; however, when loperamide-containing nanoparticles are coated with polysorbate 80 and injected, the results were the same as typical opiates and opioids -- long, effective analgesia. A solution prepared using loperamide coated with polysorbate 80 resulted in a very short duration of action and less effective analgesic effect. The same study concluded that loperamide does not cause any analgesic effects when taken by itself.

Concurrent administration of P-glycoprotein inhibitors such as quinidine with loperamide has been found to produce respiratory depression, indicative of central opioid action.