LOPRACIAN
Loperamide Tablets USP 2 mg

QUALITATIVE AND QUANTITATIVE COMPOSITION:
Label claim:
Each uncoated tablet contains:
Loperamide Hydrochloride USP 2 mg
Excipients q.s.

List of excipients:
Lactose BP
Maize Starch BP
Microcrystalline Cellulose BP
Croscarmellose Sodium BP
Povidone (PVP K-30) BP
Purified Talc BP
Magnesium Stearate BP
Colloidal Anhydrous Silica BP
Sodium Starch Glycolate BP
Sodium Bicarbonate BP

INDICATION:
For the symptomatic treatment of acute diarrhoea in adults and children aged 12 years and over.
For the symptomatic treatment of acute episodes of diarrhoea associated with Irritable Bowel Syndrome in adults aged 18 years and over following initial diagnosis by a doctor.

PHARMACEUTICAL FORM:
White coloured, round, biconvex, uncoated tablet plain on both sides.

DOSAGE AND ADMINISTRATION:
Acute diarrhoea:
Adults, the elderly, and children 12 years and over:
Two tablets (4 mg) initially followed by 1 tablet (2 mg) after every loose stool. The maximum daily dose should not exceed 6 tablets (12 mg).
Symptomatic treatment of acute episodes of diarrhoea associated with irritable bowel syndrome
Adults aged 18 years and over:
Two tablets (4 mg) initially, followed by 1 tablet (2 mg) after every loose stool, or as previously advised by your doctor. The maximum daily dose should not exceed 6 tablets (12 mg).
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, Lopracian should be used with caution in such patients because of reduced first pass metabolism.
Method of administration:
Oral use. Allow the tablet to disintegrate on the tongue and swallow the medication.

CONTRAINDICATION:
Lopracian Tablets are contra-indicated:
- In patients with a known hypersensitivity to loperamide hydrochloride or to any of the excipients.
- In children less than 12 years of age.
- 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.

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

SPECIAL WARNING AND PRECAUTION FOR USE:
Treatment of diarrhoea with Lopracian is only symptomatic. Whenever an underlying etiology can be determined, specific treatment should be given when appropriate. The priority in acute diarrhoea is the prevention or reversal of fluid and electrolyte depletion. This is particularly important in young children and in frail and elderly patients with acute diarrhoea. Use of LOPRACIAN does not preclude the administration of appropriate fluid and electrolyte replacement therapy.
Since persistent diarrhoea can be an indicator of potentially more serious conditions, this medicine should not be used for prolonged periods until the underlying cause of the diarrhoea has been investigated.
In acute diarrhoea, if clinical improvement is not observed within 48 hours, the administration of Lopracian should be discontinued and patients should be advised to consult their doctor.
Patients with AIDS treated with Lopracian 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.
Although no pharmacokinetic data are available in patients with hepatic impairment, Lopracian should be used with caution in such patients because of reduced first pass metabolism, as it may result in a relative overdose leading to CNS toxicity.
If patients are taking this medicine to control episodes of diarrhoea associated with Irritable Bowel Syndrome previously diagnosed by their doctor, and clinical improvement is not observed within 48 hours, the administration of loperamide HCl should be discontinued and they should consult with their doctor. Patients should also return to their doctor if the pattern of their symptoms changes or if the repeated episodes of diarrhoea continue for more than two weeks.

ADVERSE REACTION:
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 display 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).

System Organ Class	Adverse Drug Reactions		
	Frequency Category		
	Common	Uncommon	Not Known
Immune System Disorders			Hypersensitivity reaction Anaphylactic reaction (including Anaphylactic shock) Anaphylactoid reaction
Nervous System Disorders	Headache	Dizziness Somnolence	Loss of consciousnessa Stupora Depressed level of consciousnessa Hypertoniaa Coordination abnormality
Eye Disorders			Miosis
Gastrointestinal Disorders	Constipation Nausea Flatulence	Abdominal pain Abdominal discomfort Dry mouth Abdominal pain upper Vomiting Dyspepsia	Ileus (including paralytic ileus) Megacolon (including toxic megacolon) Glossodynia Abdominal distension
Skin and Subcutaneous Tissue Disorders		Rash	Bullous eruption (including Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme) Angioedema Urticaria Pruritus
Renal and Urinary Disorders			Urinary retention
General Disorders and Administration Site Conditions			Fatigue

INTERACTION WITH OTHER MEDICINE AND CONCOMITANT USE:
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 loperamide (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. These increases were not associated with central nervous system (CNS) effects as measured by psychomotor tests (i.e. subjective drowsiness and the Digit Symbol Substitution Test).
The concomitant administration of loperamide (16 mg single dose) and ketoconazole, an inhibitor of CYP3A4 and P-glycoprotein, resulted in a 5-fold increase in loperamide plasma concentrations. This increase was not associated with increased pharmacodynamic effects as measured by pupillometry.
Concomitant treatment with oral desmopressin resulted in a 3-fold increase of desmopressin plasma concentrations, presumably due to slower gastrointestinal motility.
It is expected that drugs with similar pharmacological properties may potentiate loperamide's effect and that drugs that accelerate gastrointestinal transit may decrease its effect.

PREGNANCY AND LACTATION:
Safety in human pregnancy has not been established, although from animal studies there are no indications that loperamide HCl possesses any teratogenic or embryotoxic properties. As with other drugs, it is not advisable to administer loperamide in pregnancy, especially during the first trimester.
Small amounts of loperamide may appear in human breast milk. Therefore loperamide is not recommended during breast-feeding.
Women who are pregnant or breast-feeding should therefore be advised to consult their doctor for appropriate treatment.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:
Loss of consciousness, depressed level of consciousness, tiredness, dizziness, or drowsiness may occur when diarrhoea is treated with loperamide. Therefore, it is advisable to use caution when driving a car or operating machinery.

OVERDOSE:
Symptoms:
In case of overdose (including relative overdose due to hepatic dysfunction), CNS depression (stupor, coordination abnormality, somnolence, miosis, muscular hypertonia and respiratory depression), constipation, urinary retention and ileus may occur. Children, and patients with hepatic dysfunction, may be more sensitive to CNS effects.
Treatment:
If symptoms of overdose occur, naloxone can be given as an antidote. Since the duration of action of loperamide 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:
PHARMACOKINETICS:
Absorption
Most ingested loperamide is absorbed from the gut, but as a result of significant first pass metabolism, systemic bioavailability is only approximately 0.3%.
Distribution
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. The plasma protein binding of loperamide is 95%, mainly to albumin. Non-clinical data have shown that loperamide is a P-glycoprotein substrate.
Metabolism
Loperamide is almost completely extracted by the liver, where it is predominantly metabolized, conjugated and excreted via the bile. Oxidative N-demethylation is the main metabolic pathway for loperamide, and is mediated mainly through CYP3A4 and CYP2C8. Due to this very high first pass effect, plasma concentrations of unchanged drug remain extremely low.
Elimination
The half-life of loperamide in man is about 11 hours with a range of 9-14 hours. Excretion of the unchanged loperamide and the metabolites mainly occurs through the faeces.

PHARMACODYNAMICS:
Pharmacotherapeutic group: Antipropulsives
ATC code: A07DA03
Loperamide binds to the opiate receptor in the gut wall, reducing propulsive peristalsis, increasing intestinal transit time and enhancing resorption of water and electrolytes. Loperamide increases the tone of the anal sphincter, which helps reduce faecal incontinence and urgency.
In a double blind randomised clinical trial in 56 patients with acute diarrhoea receiving loperamide, onset of anti-diarrhoeal action was observed within one hour following a single 4 mg dose. Clinical comparisons with other anti-diarrhoeal drugs confirmed this exceptionally rapid onset of action of loperamide.

PACKAGING:
10 tablets are packed in an Alu-PVC blister and such 10 blisters are packed in a printed carton along with pack insert.

STORAGE CONDITION:
Store in dry place below 30°C. Keep out of reach of children.

SHELF LIFE:
36 Months

MANUFACTURED BY:
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