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INSTRUCTION
for medical use

LOFLATIL®

Composition:
active substance: loperamide hydrochloride, simethicone;
1 tablet contains loperamide hydrochloride 2 mg, simethicone 125 mg;
excipients: microcrystalline cellulose, magnesium aluminium silicate, lactose monohydrate, calcium hydrogen phosphate, colloidal anhydrous silica, povidone K-30, stearic acid, croscarmellose sodium, Opadry II 85G52482 yellow: polyvinyl alcohol, talc, titanium dioxide (E 171), polyethylene glycol, lecithin, iron oxide yellow (E 172).

Pharmaceutical form. Film coated tablets.
Basic physical and chemical properties: yellow, capsule shaped, film coated tablets with a break line on one side.

Pharmacotherapeutic group.
Antidiarrheals; intestinal anti-inflammatory/anti-infective agents. Antipropulsives. Loperamide, combinations. ATC code: A07D A53.

Pharmacological properties.
Pharmacodynamics.
Loflatil® is a combination drug that combines two drugs: loperamide hydrochloride and simethicone.
Mechanism of action of loperamide hydrochloride.
Loperamide hydrochloride binds to the opiate receptor in the gut wall. Consequently, it inhibits the release of acetylcholine and prostaglandins, thereby reducing propulsive peristalsis, increasing intestinal transit time of the intestinal contents, and enhancing resorption of water and electrolytes by the intestinal wall. Loperamide hydrochloride increases the tone of the anal sphincter, thereby reducing incontinence and urgency.
Mechanism of action of simethicone.
Simethicone is a non-toxic inert surface-active agent with defoaming properties which relieves symptoms associated with diarrhea, particularly flatulence, abdominal discomfort, bloating and cramping. Simethicone is a liquid dimethicone activated by fine silicon dioxide to enhance the properties of the silicone defoamer.
Pharmacokinetics.

Loperamide hydrochloride.
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 loperamide 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.
Paediatric population. No pharmacokinetic studies were performed in the paediatric population. It is expected that pharmacokinetic behaviour of loperamide and drug-drug interactions with loperamide will be similar to those in adults.
Simethicone.
Simethicone is physiologically and chemically inert substance, it is not absorbed and is eliminated unchanged after passing through the gastrointestinal tract.

Clinical characteristics.

Indications.

Symptomatic treatment of acute diarrhea in adults and children above 12 years old accompanied with abdominal discomfort, including bloating, spasmodic pain and meteorism.

Contraindications.

Loflatil® is contraindicated to:

- patients with a known hypersensitivity to loperamide hydrochloride, simethicone or to any of the excipients;
- children under 12 years old;
- patients with acute dysentery, characterized by the presence of blood in the stool and high fever;
- patients with acute ulcerative colitis;
- patients with pseudomembranous colitis associated with the use of broad-spectrum antibiotics;
- patients with bacterial enterocolitis caused by *Salmonella*, *Shigella* and *Campylobacter* microorganisms;
- patients with intestinal obstruction or obstructive diseases of the gastrointestinal tract.

Loflatil® should not be used when the inhibition of peristalsis is to be avoided due to the possible risk of significant sequelae including ileus, megacolon, and toxic megacolon.
The drug must be discontinued promptly when constipation, abdominal distension or ileus develop.

Interaction with other medicinal products and other forms of interaction.

Interactions associated with loperamide hydrochloride.
Cases of interaction with drugs having similar pharmacological properties have been reported. Medicines that have a depressing effect on the central nervous system should not be used simultaneously with Loflatil® in children.
Non-clinical data have shown that loperamide is a P-glycoprotein substrate. Concomitant administration of loperamide (16 mg 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, 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.
Interactions associated with simethicone.
Levothyroxine may bind to simethicone. Absorption of levothyroxine in the intestine may be impaired if given concurrently with simethicone.

Special warnings and precautions for use.
Treatment of diarrhea with loperamide hydrochloride is only symptomatic. Whenever an underlying etiology can be determined, specific treatment should be given when appropriate.
Dehydration and electrolyte imbalance
Dehydration and electrolyte imbalance may occur in patients with diarrhea, especially in its severe course, as well as in children, weakened elderly patients. In such cases, an important therapeutic measure is the introduction of an appropriate amount of fluid and restoration of the electrolyte balance.
The use of the drug does not replace the introduction of an appropriate amount of fluid and restoration of the electrolyte balance.
Because persistent diarrhea may indicate potentially more serious conditions, the drug should not be used for long periods of time until the cause of the diarrhea is investigated.
In case of acute diarrhea, when there is no clinical improvement within 48 hours, the use of Loflatil® should be stopped and a doctor should be consulted.
Loperamide should not be used when the inhibition of peristalsis is to be avoided due to the possible risk of significant sequelae including megacolon and toxic megacolon.
Patients with acquired immunodeficiency syndrome (AIDS)
Patients with AIDS treated with Loflatil® for diarrhea should have therapy stopped at the earliest signs of abdominal distension. There have been isolated reports of ileus with an increased risk for toxic megacolon in AIDS patients with infectious colitis from both viral and bacterial pathogens treated with loperamide hydrochloride.
Patients with hepatic impairment
Although no pharmacokinetic data are available in patients with hepatic impairment, Loflatil® should be used with caution in such patients because of reduced first pass metabolism. This drug should be used carefully in patients with impaired liver function, as this might result in a relative overdose leading to CNS toxicity. Loflatil® should be used under medical supervision in patients with severe liver dysfunction. Medicines that prolong the transit time can lead to the development of toxic megacolon in this group of patients.
Patients with renal impairment

Since it has been reported that loperamide is well metabolized and metabolites or the unchanged drug are excreted mainly in the faeces, Loflatil® dosage adjustments in patients with renal impairment are not required.

Overdose

Within its therapeutically relevant concentration range, loperamide usually causes no significant cardiac effects. However, at extremely high concentrations associated (up to 47-fold), loperamide has cardiac actions consisting of inhibition of potassium (hERG) and sodium currents, and arrhythmias in animal models *in vivo* and *in vitro*.

Cardiac events including QT interval and QRS complex prolongation, *torsades de pointes* have been reported in association with overdose. Some cases had a fatal outcome (see "Overdose" section). Overdose can unmask existing Brugada syndrome. Patients should not exceed the recommended dose and duration of treatment.

Abuse or misuse of loperamide as an opioid substitute has been described in individuals with opioid addiction.

Loflatil® should be used with caution in patients with impaired renal or hepatic function because of the risk of accumulation and toxicity (metabolic acidosis).

Excipients

Since the drug contains lactose, it should not be used in patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption syndrome.

Use during pregnancy and lactation.

The drug is not recommended in patients who are pregnant or breast-feeding, because of the risk of accumulation and toxicity (metabolic acidosis). Women who are pregnant or breast-feeding infants should therefore be advised to consult their doctor for appropriate treatment.

Effects on ability to drive and use machines.

During treatment, you should refrain from driving vehicles or working with other machines.

Administration and dosage.

The tablets are swallowed whole with water.

Adults.

The initial dose is 2 tablets once, followed by 1 tablet after each further episode of defecation up to a maximum of 4 in 24 hours. The duration of treatment is not more than 2 days.

Children aged 12 to 18 years old.

The initial dose is 1 tablet once, followed by 1 tablet after each further episode of defecation up to a maximum of 4 in 24 hours. The duration of treatment is not more than 2 days.

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, Loflatil® should be used with caution in such patients because of reduced first pass metabolism (see "Special warnings and precautions for use" section).

Paediatric population.

The drug is contraindicated in patients under 12 years of age.

Overdose.

Symptoms.

In case of overdose (including overdose due to hepatic dysfunction), CNS depression (stupor, coordination abnormality, somnolence, miosis, muscular hypertonia and respiratory depression), dry mouth, abdominal discomfort, nausea, vomiting, constipation, urinary retention, and paralytic ileus may occur.

Children, and patients with hepatic dysfunction, may be more sensitive to CNS effects. In children, depression of the central nervous system may occur more often.

In individuals who have ingested overdoses of loperamide, cardiac events such as QT interval and QRS complex prolongation, *torsades de pointes*, other serious ventricular arrhythmias, cardiac arrest and syncope have been observed. Fatal cases have also been reported. Overdose can unmask existing Brugada syndrome.

Treatment.

If overdose occurs, the patient should immediately consult a doctor.

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

If symptoms of overdose occur, naloxone may be given as an antidote. Since the half-life period of loperamide is longer than that of naloxone (1 to 3 hours), repeated treatment with naloxone might be indicated. 24-hour monitoring of respiratory function is necessary. The patient should be kept under constant observation for at least 48 hours in order to detect any possible depression of the central nervous system.

Adverse reactions.

The following classification is used to assess the frequency of adverse reactions: 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), very rare (<1/10,000), including isolated cases, not known (cannot be estimated from the available data).

Immune system disorders.

Rare: hypersensitivity reaction, anaphylactic reaction (including anaphylactic shock), anaphylactoid reactions.

Skin and subcutaneous tissue disorders.

Uncommon: rash.

Rare: urticaria, pruritus, angioedema, facial swelling, tongue swelling and difficulty breathing, bullous eruption (including Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis).

Gastrointestinal disorders.

Common: nausea.

Uncommon: dry mouth, constipation, abdominal pain, abdominal discomfort, vomiting, dyspepsia, flatulence.

Rare: megacolon (including toxic megacolon), intestinal obstruction (including paralytic ileus), abdominal distention.

Not known: acute pancreatitis.

Nervous system disorders.

Common: headache, dysgeusia (change in taste sensation).

Uncommon: drowsiness, dizziness.

Rare: depressed level of consciousness, loss of consciousness, stupor, hypertonia, coordination abnormality.

Renal and urinary disorders.

Rare: urinary retention.

Eye disorders.
Rare: miosis.
General disorders.
Uncommon: asthenia.
Rare: increased fatigue.
Reporting of suspected adverse reactions.
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Medical and pharmaceutical workers, as well as patients or their legal representatives are asked to report any suspected adverse reactions and lack of effectiveness of the medicinal product through the Pharmacovigilance Automated Information System at: https://aisf.dec.gov.ua.

Shelf life. 3 years.

Storage conditions.
Store in the original package at the temperature not more than 25°C.
Keep out of reach of children.

Package.
10 tablets in a blister, 1 blister in a carton package.
10 tablets in a strip, 1 strip in a carton package.
10 tablets in a blister, 1 blister in a carton package, 10 packages in a carton box.
10 tablets in a strip, 1 strip in a carton package, 10 packages in a carton box.
10 tablets in a blister, 10 blisters in a carton package.

Condition of supply.
Without prescription:
10 tablets in a blister, 1 blister in a carton package.
10 tablets in a strip, 1 strip in a carton package.
By prescription:
10 tablets in a blister, 1 blister in a carton package, 10 packages in a carton box.
10 tablets in a strip, 1 strip in a carton package, 10 packages in a carton box.
10 tablets in a blister, 10 blisters in a carton package.

Manufacturer.
KUSUM HEALTHCARE PVT LTD.

Location of manufacturer and its address of business activity.
SP-289 (A), RIICO Industrial area, Chopanki, Bhiwadi, Dist. Alwar (Rajasthan), India.

Date of last revision.