Professional Information

SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

LOPERASTAT® SYRUP

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml Syrup contains:

Loperamide hydrochloride	1 mg
Alcohol	1,4 % *v/v*

Sugar free, artificially sweetened.

PRESERVATIVES:

Methylparahydroxybenzoate	0,072 % *m/v*
Propylparahydroxybenzoate	0,008 % *m/v*

3. PHARMACEUTICAL FORM

Syrup

Clear, reddish-pink coloured syrup with a fruity flavour.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

LOPERASTAT® SYRUP is indicated for symptomatic relief of acute and chronic non specific diarrhoea and to inhibit peristalsis and slow intestinal transit time in patients with iloestomies, colostomies and other intestinal resections.

For children under the age of 6 years:

LOPERASTAT® SYRUP is indicated for inhibition of peristalsis and slowing of intestinal transit time.

4.2 Posology and method of administration

ACUTE NON SPECIFIC DIARRHOEA:

One medicine measure (5 ml) per 12,5 kg body mass followed by half medicine measure (2,5 ml) per 12,5 kg after each subsequent loose stool.

Daily dosage should not exceed three medicine measures (15 ml) per 12,5 kg body mass.

Weight in kilograms (kg)	**Initial dose (ml)**	**On subsequent loose stools**	**Maximum daily dose**
10 - 14,9	5 ml	2,5 ml	15 ml
15 - 19,9	7,5 ml	*3,7 ml	20 ml
20	10 ml	5 ml	30 ml
40	15 ml	7,5 ml	60 ml
70	20 ml	10 ml	80 ml

* 3, 7 ml is equal to 3/4 of a medicine measure.

IMPORTANT

Stop **LOPERASTAT® SYRUP** as soon as diarrhoea is under control.

In acute diarrhoea, if clinical improvement is not observed within 48 hours, the administration of **LOPERASTAT® SYRUP** should be discontinued and patients should be advised to consult their doctor.

CHRONIC NON-SPECIFIC DIARRHOEA: (Consult your doctor)

With individual adjusted dosage it is usually possible to obtain a virtually normal bowel movement.

Starting dose is 1 medicine measure (5 ml) per 12, 5 kg body mass a day for children.

The daily dose should be adjusted until 1-2 solid stools per day are obtained. This is usually achieved on a maintenance dose of ½ - 2 medicine measures (2,5 ml – 10 ml) daily.

If constipation occurs, the dosage should be decreased.

Elderly

No dose adjustment is required for the elderly.

Hepatic impairment

Although no pharmacokinetic data are available in patients with hepatic impairment, **LOPERASTAT® SYRUP** should be used with caution in such patients because of reduced first pass metabolism. (see Section 4.4).

Method of Administration

For oral use.

4.3 Contraindications

- **LOPERASTAT® SYRUP** is contraindicated in patients with a known hypersensitivity to the active substance, loperamide hydrochloride or to any of the excipients listed in **section 6.1**
- **LOPERASTAT® SYRUP** is contraindicated in infants below 24 months of age
- **LOPERASTAT® SYRUP** should not be used as the primary therapy in patients with acute dysentery, which is characterised by blood in stools and high fever
- **LOPERASTAT® SYRUP** must not be used:
    - 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, LOPERASTAT® SYRUP 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.

LOPERASTAT® SYRUP must be discontinued promptly when constipation, abdominal distension or ileus develop.

Treatment of diarrhoea with **LOPERASTAT® SYRUP** is only symptomatic. Whenever an underlying etiology can be determined, specific treatment should be given when appropriate (or when indicated).

4.4 Special warnings and precautions for use

In patients with diarrhoea, especially in infants, fluids and electrolyte depletion may occur. In such cases administration of appropriate fluid and electrolyte replacement (oral rehydration therapy) [ORT] is the most important measure.

LOPERSTAT® SYRUP should not be given to children less than 6 years of age without a medical prescription and supervision. **LOPERSTAT® SYRUP** is not recommended for routine use in acute or chronic diarrhoea in children under the age of 6 years.

Patients with AIDS treated with LOPERASTAT® SYRUP for diarrhoea should have therapy stopped at the earliest signs of abdominal distension. There have been reports of toxic megacolon in

AIDS patients with infectious colitis from both viral and bacterial pathogens treated with LOPERASTAT® SYRUP.

Although no pharmacokinetic data are available in patients with hepatic impairment, **LOPERASTAT® SYRUP** 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 central nervous system toxicity.

In acute diarrhoea, if clinical improvement is not observed within 48 hours, the administration of **LOPERASTAT® SYRUP** should be discontinued and patients should be advised to consult their doctor.

Patients with hepatic dysfunction should be monitored closely for signs of Central Nervous System toxicity because of the high first-pass metabolism.

Cardiac events including QT and QRS complex prolongation, torsade de pointes have been reported in association with overdose. Some cases had a fatal outcome (see section 4.9). Overdose can unmask existing Brugada syndrome. Patients should not exceed the recommended dose and/or the recommended duration of treatment.

LOPERASTAT® SYRUP contains:

- Glycerol which may cause headache, stomach upset and diarrhoea.
- Methylparahydroxybenzoate and propylparahydroxybenzoate may cause allergic reactions (possibly delayed).
- Small amounts of ethanol (alcohol), less than 100 mg per dose.

4.5 Interaction with other medicines and other forms of interaction

Non-clinical data have shown that loperamide is a P-glycoprotein substrate. Concomitant administration of loperamide (16 mg single dose) with quinidine, or navir, 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 (2 mg, up to 16 mg maximum daily dose), 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 CYP2C8inhibitor, 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.

The concomitant administration of loperamide with oral desmopressin may result 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 which elerate gastrointestinal transit may decrease its effect.

4.6 Fertility, pregnancy and lactation

The safety of use during pregnancy and lactation has not been established.

Small amounts of loperamide may appear in human breast milk. Therefore, **LOPERSTAT® SYRUP** is not recommended during breastfeeding.

Women who are breast feeding infants should therefore be advised to consult their doctor for appropriate treatment.

4.7 Effects on ability to drive and use machines

Tiredness, dizziness, or drowsiness may occur in the setting of diarrhoeal syndromes treated with **LOPERSTAT® SYRUP**. Therefore, it is advisable to use caution when driving a car or operating machinery. See section 4.8.

4.8 Undesirable effects

System Organ Class (SOC)	**Adverse Drug Reaction**	**Frequency**
Immune System Disorders	Hypersensitivity reaction, Anaphylactic reaction (including	Less frequent
Nervous System Disorders	Headache, Dizziness	Frequent
	Somnolence	Less frequent

	Loss of consciousness, Stupor, Depressed level of consciousness, Hypertonia, Coordination abnormality	Less frequent
Eye Disorders	Miosis	Less frequent
Gastrointestinal Disorders	Constipation, Nausea, Flatulence	Frequent
	Abdominal pain, Abdominal discomfort, Dry mouth, Abdominal pain upper, Vomiting, Dyspepsia, acute pancreatitis	Less frequent
	Ileus (including paralytic ileus), Megacolon (including toxic megacolon – see section 4.4), Abdominal distension	Less frequent
Skin and Subcutaneous Tissue Disorders	Rash, Bullous eruption (including Stevens-Johnson syndrome, Toxic epidermal necrolysis and Erythema multiforme), Angioedema, Urticaria, Pruritus	Less frequent
Renal and Urinary Disorders	Urinary retention	Less frequent
General Disorders and Administration Site Conditions	Fatigue	Less frequent

A number of the adverse reactions reported during the clinical investigations and post-marketing experience with loperamide hydrochloride are frequent symptoms of the underlying diarrhoeal syndrome (for example abdominal pain/discomfort, nausea, vomiting, dry mouth, tiredness, drowsiness, dizziness, constipation, and flatulence). These symptoms are often difficult to distinguish from undesirable drug effects.

Paediatric population

The safety of loperamide hydrochloride was evaluated in 607 patients aged 10 days to 13 years, who participated in 13 controlled and uncontrolled clinical trials of loperamide hydrochloride used for the treatment of acute diarrhoea. In general, the adverse reactions profile in this patient population was similar to that seen in clinical trials of loperamide hydrochloride in adults and children aged 12 years and over.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care provders are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Convulsions have been reported in children under the age of two years.

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 andileus may occur. Children and patients with hepatic dysfunction may be more sensitive to CNS effects than adults.

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 (see section 4.4). Fatal cases have also been reported. Overdose can unmask existing Brugada syndrome.

Treatment

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

If the patient develops respiratory depression, airway obstruction, vomiting with impaired consciousness or other CNS symptoms of overdose, give naloxone urgently. 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. Other measures should be as indicated by the patient's clinical condition.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A.11.9 Medicines acting on the gastro-intestinal tract. Antidiarrhoeals

Pharmacotherapeutic Group: Antipropulsives; ATC code: A07DA03

LOPERASTAT® SYRUP inhibits hypermotility by direct action on the bowel wall. Its inhibition of peristalsis is the result of decreasing the activity of both the longitudinal muscles (preparatory and reflex phases) and the circular muscles (reflex phase).

5.2 Pharmacokinetic properties

LOPERASTAT® SYRUP is incompletely absorbed from the gut and it is almost completely metabolized in the liver where it is conjugated and excreted via the bile.

LOPERASTAT® SYRUP is mainly eliminated via the faeces.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Ethanol 96 % *v/v*,
- Glycerol,
- Hydrochloric Acid Solution,
- Methylparahydroxybenzoate
- Pineapple Fruity Flavour F379,
- Propylparahydroxybenzoate
- Raspberry Essence No.1,
- Raspberry Red Powder,
- Sodium Cyclamate,
- Sodium Hydroxide Solution.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 ^{o}C. Protect from light.

6.5 Nature and contents of container

Amber glass bottle containing 50 ml and 100 ml of the liquid.

6.6 Special precautions for disposal

This medicinal product does not require any special storage conditions.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals (Pty) Ltd

14 Lautre Road

Stormill Ext.1

Roodepoort, 1724

South Africa

8. REGISTRATION NUMBER(S)

28/11.9/0649 (S.A.)

S2 BOT 0500757 (Botswana) (50 ml)

NS1 04/11.9/0996 (Namibia) (50 ml)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19 April 1995

10. DATE OF REVISON OF THE TEXT

14 March 2023