SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

KRISMOTIL TABLETS (Loperamide Hydrochloride Tablets BP 2 mg)

2. QUALITATIVE AND QUANTITATIVECOMPOSITION

Each uncoated tablet contains:
Loperamide hydrochloride BP 2 mg
Excipients Q.S.

3. PHARMACEUTICAL FORM

Tablets

White coloured, Circular flat uncoated tablets with a break-line on one side and plan on other side.

4. Clinical particulars

4.1 Therapeutic indications

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 Trritable Bowel Syndrome in adult aged 18 years and over following initial diagnosis by a doctor.

4.2 Posology and method ofadministration

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, loperamide tablets should be used with caution in such patients because of reduced first pass metabolism.
Method of administration:
Oral use.

4.3 Contraindications

Loperamide tablets is contraindicated:

• 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.

Loperamide tablets 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.

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

4.4 Special warnings and precautions for use

Treatment of diarrhoea with Loperamide tablets 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 Loperamide tablets 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 Loperamide tablets should be discontinued and patients should be advised to consult their doctor.

Patients with AIDS treated with Loperamide tablets 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, Loperamide tablets 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.

4.5 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.

4.6 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.

4.7 Undesirable effects

Adults and children aged ≥ 12 years

The safety of loperamide HCl was evaluated in 2755 adults and children aged ≥ 12 years who participated in 26 controlled and uncontrolled clinical trials of loperamide HCl used for the treatment of acute diarrhoea.

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 displays 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).

Adverse Drug reactions

System Organ Class	**Indication**		
	Common	**Uncommon**	**Rare**
Immune System Disorders			Hypersensitivity reaction Anaphylactic reaction (including Anaphylactic shock) Anaphylactoid reaction
Nervous System Disorders	Headache	Dizziness Somnolence	Loss of consciousness Stupor Depressed level of consciousness Hypertonia Coordination abnormality
Eye Disorders			
Gastrointestinal Disorders	Constipation Nausea Flatulence	Abdominal pain Abdominal discomfort	Ileus (including paralytic ileus) Megacolon (including

Skin and Subcutaneous Tissue Disorders		Dry mouth Abdominal pain upper Vomiting Dyspepsia Rash	toxic megacolon) Glossodynia Abdominal distension Bullous eruption (including Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme) Angioedema Urticaria Pruritus
Renal and Urinary Disorders **General Disorders and Administration Site Conditions**			Urinary retention Fatigue

4.8 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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.

5.2 Pharmacokinetic properties

In man, Loperamide hydrochloride prolongs the transit time of the intestinal contents. It reduces the daily fecal volume, increases the viscosity and bulk density, and diminishes the loss of fluid and electrolytes. Tolerance to the antidiarrheal effect has not been

observed. Clinical studies have indicated that the apparent elimination half-life of Loperamide hydrochloride in man is 10.8 hours with a range of 9.1 to 14.4 hours. Plasma levels of unchanged drug remain below 2 nanograms per mL after the intake of a 2 mg Loperamide hydrochloride. Plasma levels are highest approximately five hours after administration of the tablet and 2.5 hours after the liquid. The peak plasma levels of Loperamide were similar for both formulations. Elimination of Loperamide mainly occurs by oxidative N-demethylation. Cytochrome P450 (CYP450) isozymes, CYP2C8and CYP3A4, are thought to play an important role in Loperamide N-demethylation process since quercetin (CYP2C8 inhibitor) and ketoconazole (CYP3A4 inhibitor) significantly inhibited the N-demethylation process in vitro by 40% and 90%, respectively. In addition, CYP2B6 and CYP2D6 appear to play a minor role in Loperamide N-demethylation. Excretion of the unchanged Loperamide and its metabolites mainly occurs through the feces. In those patients in whom biochemical and hematological parameters were monitored during clinical trials, no trends toward abnormality during Loperamide hydrochloride therapy were noted.

5.3 Preclinical safety data

Acute and chronic studies on loperamide showed no specific toxicity. Results of in vivo and in vitro studies carried out indicated that loperamide is not genotoxic. In reproduction studies, very high doses (40 mg/kg/day – 240 times the maximum human use level) loperamide impaired fertility and foetal survival in association with maternal toxicity in rats. Lower doses had no effects on maternal or foetal health and did not affect peri- and post-natal development.

Non-clinical in vitro and in vivo evaluation of Loperamide indicates no significant cardiac electrophysiological effects within its therapeutically relevant concentration range and at significant multiples of this range (up to 47-fold). However, at extremely high concentrations associated with overdoses (see section 4.4), Loperamide has cardiac electrophysiological actions consisting of inhibition of potassium (hERG) and sodium currents, and arrhythmias.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dibasic calcium Phosphate BP
PVPK-90 BP
Sodium Mehtyl Paraben BP
Sodium Propyl Paraben BP
Sodium Starch Glycollate BP
Maize Starch BP
Purified Talc BP
Magnesium stearate BP

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store in a temperature below 30 °C, protect from light and moisture.

Protect from light and moisture.

6.5 Nature and contents of container

Product is packed in 20x5x10 Tablets strip pack in a printed carton along with insert.

6.6 Special precautions for disposal

No special requirements

7. MARKETING AUTHORISATION HOLDER

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