**National Agency for Food & Drug Administration & Control (NAFDAC)**

**Registration & Regulatory Affairs (R & R) Directorate**

# SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

## 1. 1. NAME OF THE MEDICINAL PRODUCT

KOYOTIL CAPSULES
**(LOPERAMIDE HYDROCHLORIDE CAPSULES USP 2 MG)**

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

| Sr. No. | Name of Ingredient | Category | Specification | Quantity Per Unit Dose (mg) | Required Quantity (KG) |
|---|---|---|---|---|---|
| 1. | Loperamide Hydrochloride BP | API | BP | 2.060 | 3.193 |
| 2. | Maize Starch | Diluents | BP | 24.940 | 38.657 |
| 3. | Lactose | Diluents | BP | 77.500 | 120.125 |
| 4. | Dibasic Calcium Phosphate | Diluents | BP | 25.000 | 38.750 |
| 5. | Sodium Lauryl Sulphate | Surfactant | BP | 1.000 | 1.550 |
| 6. | Colloidal Silicon Dioxide (Aerosil) | Glidant | BP | 1.500 | 2.325 |
| 7. | Sodium Starch Glycollate | Gelling Agent | BP | 2.000 | 3.100 |
| 8. | Magnesium Stearate | Lubricant | BP | 1.000 | 1.550 |
| | | | Total Filled weight | 135 mg | 209.5 kgs |
| 9. | E. H.G. Capsules size “4” empty hard gelatin capsule with “Green” colored cap & “Gray” colored body. | Capsules shell | In-house | 40 mg | 15, 81, 000 Nos. |
| | **Total weight of capsule** | | | **175.00 mg** | **271.250 kgs** |

## 3. PHARMACEUTICAL FORM

Hard gelatin Capsules
**Description:** Size “4” hard gelatin capsule with “Green” coloured cap & “Grey” coloured body, filled with white colour powder.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

For the symptomatic treatment of acute diarrhoea, in adults and children 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.

### 4.2 Posology and method of administration

Posology:

**Acute Diarrhoea**

Adults and children over 12:

Two capsules (4 mg) initially, followed by one capsule (2 mg) after each loose stool.

The usual dose is 3-4 capsules (6 mg – 8 mg) a day. The total daily dose should not exceed 6 capsules (12 mg).

**Symptomatic treatment of acute episodes of diarrhoea associated with irritable bowel**

**syndrome in adults aged 18 and over**

Two capsules (4 mg) to be taken initially, followed by 1 capsule (2 mg) after every loose stool, or as previously advised by your doctor. The maximum daily dose should not exceed 6 capsules (12 mg).

**Paediatric population**

Loperamide hydrochloride is contraindicated in children less than 12 years of age.

**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 hydrochloride should be used with caution in such patients because of reduced first pass metabolism (see section 4.4 Special warnings and precautions for use).

Method of administration

Oral use. The capsules should be taken with liquid.

### 4.3 Contraindications

This medicine is contraindicated:

• in patients with hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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

### 4.4 Special warnings and precautions for use

Treatment of diarrhoea with loperamide hydrochloride 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 this medicine 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 hydrochloride should be discontinued and patients should be advised to consult their doctor.

Patients with AIDS treated with this medicine 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, this medicine 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.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine because it contains lactose.

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.

Cardiac events including QT prolongation and torsades de pointes have been reported in association with overdose. Some cases had a fatal outcome (see section 4.9). Patients should not exceed the recommended dose and/or the recommended duration of treatment.

**Special Warnings to be included on the leaflet:**

Only take Loperamide Capsules to treat acute episodes of diarrhoea associated with Irritable Bowel Syndrome if your doctor has previously diagnosed IBS.

If any of the following now apply, do not use the product without first consulting your doctor, even if you know you have IBS:

• If you are aged 40 or over and it is some time since your last IBS attack

• If you are aged 40 or over and your IBS symptoms are different this time

• If you have recently passed blood from the bowel

• If you suffer from severe constipation
• If you are feeling sick or vomiting
• If you have lost your appetite or lost weight
• If you have difficulty or pain passing urine
• If you have a fever
• If you have recently travelled abroad

Consult your doctor if you develop new symptoms, if your symptoms worsen, or if your symptoms have not improved over two weeks.

**4.5 Interaction with other medicinal products 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 ritonavir, which are both P-glucoprotein 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.

**4.6 Pregnancy and lactation**

Pregnancy

Safety in human pregnancy has not been established, although from animal studies there are no indications that loperamide hydrochloride possesses any teratogenic or embryotoxic properties. As with other drugs, it is not advisable to administer this medicine in pregnancy, especially

during the first trimester.

Breast-feeding

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

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

**4.7 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 this medicine. Therefore, it is advisable to use caution when driving a car or operating machinery. See Section 4.8, Undesirable Effects.

**4.8 Undesirable effects**

**Adults and children aged ≥12 years**

The safety of loperamide hydrochloride 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 hydrochloride 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).

**Table 1:** ***Adverse Drug Reactions***

| System Organ Class | Indication | | |
|---|---|---|---|
| | Common | Uncommon | Rare |
| Immune System Disorders | | | Hypersensitivity reaction[a]<br>Anaphylactic reaction (including Anaphylactic shock)[a]<br>Anaphylactoid reaction[a] |
| Nervous System Disorders | Headache | Dizziness<br>Somnolence[a] | Loss of consciousness[a]<br>Stupor[a]<br>Depressed level of consciousness[a]<br>Hypertonia[a]<br>Coordination abnormality[a] |

| | | | |
|---|---|---|---|
| Eye Disorders | | | Miosis[a] |
| Gastrointestinal Disorders | Constipation<br>Nausea<br>Flatulence | Abdominal pain<br>Abdominal discomfort<br>Dry mouth<br>Abdominal pain upper<br>Vomiting<br>Dyspepsia[a] | Ileus[a] (including paralytic ileus)<br>Megacolon[a] (including toxic megacolon[b])<br>Abdominal distension |
| Skin and Subcutaneous Tissue Disorders | | Rash | Bullous eruption[a] (including Stevens-Johnson syndrome, Toxic epidermal necrolysis and Erythema multiforme)<br>Angioedema[a]<br>Urticaria[a]<br>Pruritus[a] |
| Renal and Urinary Disorders | | | Urinary retention[a] |
| General Disorders and Administration Site Conditions | | | Fatigue[a] |

A: Inclusion of this term is based on post-marketing reports for loperamide HCl. As the process for determining post marketing ADRs did not differentiate between chronic and acute indications or adults and children, the frequency is estimated from all clinical trials with loperamide HCl (acute and chronic), including trials in children ≤ 12 years (N=3683).

**4.9 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.

In individuals who have ingested overdoses of loperamide HCl, cardiac events such as QT interval 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.

**Management:**

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

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 antidiarrhoeal drugs confirmed this exceptionally rapid onset of action of loperamide.

### 5.2 Pharmacokinetic properties

*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.

## 6. Pharmaceutical Particulars

### 6.1. List of excipients

| | |
|---|---|
| Maize Starch | BP |
| Lactose | BP |
| Dibasic calcium phosphate | BP |
| Sodium Laural Sulphate | BP |
| Colloidal Silicon Dioxide | BP |
| Sodium Starch Glycollate | BP |
| Magnesium Stearate | BP |

### 6.2. Incompatibilities

None

### 6.3. Shelf life

36 Months.

### 6.4 Special precautions for storage

Store below above 30$^{o}$C.

Store in the original package, in order to protect from moisture.

### 6.5. Nature and contents of container

10 capsules packed in one Blister. Such 1 blister packed in unit printed duplex board carton along with its package insert.

### 6.6. Special Precaution for Disposal

No special requirement

## 7. APPLICANT/MANUFACTURER

**NAFDAC Reg. No. A4-9177**

MAXHEAL LABORATORIES PVT LTD
PLOT NO.- 2-7/80-85, SURSEZ,
G.I.D.C SACHIN, SURAT GUJARAT
394230, INDIA