## 1. NAME OF THE MEDICINAL PRODUCT

{[Nationally completed name] 2mg/125mg tablets}

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains loperamide hydrochloride 2 mg and simeticone equivalent to 125 mg dimeticone.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Tablet

White to off white capsule shaped tablet (approximately 16.6 x 6.8 mm) with "LO-SI" debossed on one side and '2' & '125' debossed on the opposite side at either side of a score line

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

{Nationally completed name tablets} are indicated for the symptomatic treatment of acute diarrhoea in adults and adolescents over 12 years when acute diarrhoea is associated with gas-related abdominal discomfort including bloating, cramping or flatulence.

### 4.2 Posology and method of administration

*Posology*

Adults over 18 years
Take two tablets initially, followed by one tablet after every loose stool. Not more than 4 tablets should be taken in a day, limited to no more than 2 days.

Adolescents between 12 and 18 years
Take one tablet initially, followed by one tablet after every loose stool. Not more than 4 tablets should be taken in a day, limited to no more than 2 days.

Paediatric population

{Nationally completed name tablets} must not be used in children under 12 years.

Elderly
No dosage adjustments are required for the elderly.

Renal impairment
No dosage adjustment is necessary in renal impairment.

Hepatic impairment
Although no pharmacokinetic data are available in patients with hepatic insufficiency, {nationally completed name tablets} should be used with caution in such patients because of reduced first pass metabolism (see section 4.4).

*Method of administration*
The tablets should be taken with liquid.

## 4.3 Contraindications

{Nationally completed name tablets} must not be used in:
• Children less than 12 years of age
• Patients with a known hypersensitivity to active substances or any of the excipients listed in section 6.1
• Patients with acute dysentery, which is characterised by blood in stool and high fever
• Patients with acute ulcerative colitis
• Patients with pseudomembranous colitis associated with broad spectrum antibiotics
• Patients with bacterial enterocolitis caused by invasive organisms including Salmonella, Shigella and Campylobacter

{Nationally completed name tablets} 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. It must be discontinued promptly if constipation, ileus or abdominal distension develop.

## 4.4 Special warnings and precautions for use

Treatment of diarrhoea with loperamide-simeticone is only symptomatic. Whenever an underlying etiology can be determined, specific treatment should be given when appropriate.
In patients with (severe) diarrhoea, fluid and electrolyte depletion may occur. It is important that attention is paid to appropriate fluid and electrolyte replacement.

If clinical improvement is not observed within 48 hours, the administration of {nationally completed name tablets} must be discontinued. Patients should be advised to consult their physician.

Patients with AIDS treated with {nationally completed name 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, {nationally completed name tablets} should be used with caution in such patients because of reduced first pass metabolism. This medicinal product must be used with caution in patients with hepatic impairment as it may result in a relative overdose leading to central nervous system (CNS) toxicity. {nationally completed name tablets} should be used under medical supervision in patients with severe hepatic dysfunction.

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.

## 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-glycoprotein inhibitors, resulted in a 2 to 3-fold increase in loperamide plasma concentrations. 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 measured 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 medicinal products with similar pharmacological properties may potentiate loperamide's effect and that medicinal products that accelerate gastrointestinal transit may decrease its effect.

Since simeticone is not absorbed from the gastrointestinal tract, no relevant interactions between simeticone and other medicinal products are expected.

## 4.6 Fertility, pregnancy and lactation

Pregnancy
A limited amount of data from the use of loperamide in pregnant women is available. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). Although there are no indications that loperamide hydrochloride or simethicon possesses teratogenic or embryotoxic properties, the anticipated therapeutic benefits should be weighed against potential hazards before {nationally completed name} is given during pregnancy, especially during the first trimester.

Breast-feeding
Small amounts of loperamide hydrochloride may appear in human breast milk. Therefore, {nationally completed name} is not recommended during breast-feeding.

Fertility
Only high doses of loperamide hydrochloride affected female fertility in non-clinical studies (see section 5.3).

## 4.7 Effects on ability to drive and use machines

Tiredness, dizziness and drowsiness have been reported in patients taking loperamide. If affected, patients should not drive or operate machinery.
See Section 4.8 Undesirable effects.

## 4.8 Undesirable effects

The use of loperamide plus simeticone, in the treatment of the symptoms of diarrhoea, and gas-related abdominal discomfort associated with acute diarrhoeal illness, was studied in five placebo-controlled, and active-controlled, clinical trials involving 462 adults treated with loperamide plus simeticone. The most frequently reported Adverse Drug Reactions (ADRs) associated with the use of the medicinal product in these clinical trials were nausea and dysgeusia, reported in 1.7% and 1.9% of patients, respectively, and were considered Common.
Including the above-mentioned ADRs, the following table displays ADRs that have been reported with the use of loperamide plus simeticone, or loperamide alone, from either clinical trial or post-marketing experiences. The displayed 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); Very rare (< 1/10,000), Not known (cannot be estimated from the available data).

| **System Organ Class** | **Adverse Reactions** | | |
|---|---|---|---|
| | **Frequency** | | |
| | **Common** | **Uncommon** | **Unknown** |
| **Immune system disorders** | | | Hypersensitivity including: Anaphylactic Shock, Anaphylactoid Reaction |
| **Nervous System Disorders** | | Somnolence | Loss of consciousness, Depressed level of consciousness, Dizziness |
| **Gastrointestinal disorders** (See sections 4.3 and 4.4) | Nausea, Dysgeusia | Constipation | Megacolon, including Toxic Megacolon; Ileus; Abdominal Pain; Vomiting; Abdominal Distension; Dyspepsia; Flatulence |
| **Skin and subcutaneous tissue disorders** | | Rash | Angioedema, Urticaria, Pruritus |
| **Renal and urinary disorders** | | | Urinary Retention |

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. Healthcare professionals are asked to report any suspected adverse reactions {via the national reporting system listed in Appendix V*}.

## 4.9 Overdose

*Symptoms*

In case of overdose (including relative overdose due to hepatic dysfunction), central nervous system depression (stupor, co-ordination abnormality, somnolence, miosis, muscular hypertonia, respiratory depression), dry mouth, abdominal discomfort, nausea and vomiting, constipation, urinary retention and paralytic ileus may occur. 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.

Children may be more sensitive to CNS effects than adults.

*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 may 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: Antipropulsive antidiarrheals, ATC code: A07D A53
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 does not change the physiological flora. Loperamide increases the tone of the anal sphincter. {Nationally completed name tablets} does not act centrally.
Simeticone is an inert surface-active agent with anti-foaming properties thereby potentially relieving gas-related symptoms associated with diarrhoea.

### 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%. The simeticone component of loperamide-simeticone is not absorbed.

*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.

*Biotransformation:* 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 active substance 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.

### 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 (40mg/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.

Simeticone is a member of the class of linear polydimethylsilicones, which have been in wide general and medicinal use for many years and are regarded as biologically inert and not exhibiting toxic properties and has not been the subject of specific animal toxicity studies.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Cellulose, microcrystalline (E460)
Sodium starch glycolate
Hypromellose (E464)
Povidone (E2101)
Calcium phosphate (E341)
Mannitol (E421)
Magnesium Stearate (E572)

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

2 years

### 6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

### 6.5 Nature and contents of container

Push through blisters comprising transparent PVC/ACLAR film, heat seal coating and aluminium foil.

or

Push through blisters comprising transparent PVC/PVdC film, heat seal coating and aluminium foil.

Pack sizes of 6, 8, 10, 12, 15, 16, 18, 20 and 30 tablets.
Packed in printed cardboard cartons.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal <and other handling>

No special requirements

## 7. MARKETING AUTHORISATION HOLDER

[to be completed nationally]

## 8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

## 10. DATE OF REVISION OF THE TEXT