APPENDIX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICATION

IMODIUM 2 mg, capsule

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Loperamide hydrochloride .....2.00 mg

Amount equivalent to loperamide base .....1.86 mg

For one No.4 180.00 mg capsule

Excipients with known effect: one capsule contains 127 mg of lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule.

4. CLINICAL DATA

4.1.Therapeutic indications

Symptomatic treatment of acute and chronic diarrhea.

The treatment does not include dietary measures and rehydration if it is needed.

The importance of rehydration with an intravenous or oral rehydration solute should be adapted based on the severity of the diarrhea, age and patient characteristics (associated diseases, etc.).

4.2. Dosage and method of administration

Oral route.

The capsules should be taken with water.

Reserved for adults and children over 8 years of age.

Posology

- Acute diarrhea:

The initial dosage is 2 capsules for adults and one capsule for children.

After each unformed stool, an additional tablet will be administered, without exceeding 8 tablets in 24 hours for adults, and 6 capsules for children.

- Chronic diarrhea:

1 to 3 capsules per day for adults.

1 to 2 capsules per day for children.

Elderly subjects

No dose adjustment is required.

Renal impairment

No dosage adjustment is required.

Hepatic impairment

Although no pharmacokinetic data are available in patients with hepatic impairment, loperamide HCl should be used with caution in such patients because of reduced first pass metabolism (see section 4.4).

4.3. Contraindications

- Hypersensitivity to the active substance or to one of the excipients listed in section 6.1.
- Children under 8 years of age.
- Loperamide Hydrochloride should not be used as the primary therapy in case of:
  - o acute dysentery, which is characterized by blood in stools and high fever,
  - o acute ulcerative colitis crisis,
  - bacterial enterocolitis caused by invasive organisms including *Salmonella, Shigella,* and *Campylobacter,*
  - o pseudomembranous colitis associated with the use of broad-spectrum antibiotics.
- Loperamide Hydrochloride 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. Treatment must be discontinued when constipation, abdominal distension or ileus develop.

4.4. 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.

In patients with diarrhea, especially in children, fluid and electrolyte depletion may occur. In such cases administration of appropriate fluid and electrolyte replacement therapy is an essential measure. The patient should be informed of the need to:

- rehydrate with plenty of drinks, salted or sweetened, in order compensate for the loss of fluid due to diarrhea (the average adult daily allowance of water is 2 liters),
- eat during the course of diarrhea:
  - excluding certain intakes and particularly milk, raw vegetables, fruits, green vegetables, spicy foods as well as chilled foods or beverages. favoring grilled meats, rice.

In acute diarrhea, if diarrhea persists after 2 days of treatment, patient should be advised to discontinue the use of this medicine and to consult his physician.

Behaviour should be reassessed and the need for oral or intraveinous rehydration should be considered.

Patients with Human Immunodeficiency Virus (HIV) treated with loperamide Hydrochloride for diarrhea 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 HIV infected 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 Hydrochloride 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 (CNS) toxicity.

Cardiac events including QT interval and QRS complex prolongation ,as well as torsades 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.

This medicine contains lactose. Its use is not recommended for patients exhibiting an intolerance to lactose, Lapp lactase deficiency or glucose or galactose malabsorption syndrome (rare hereditary diseases).

4.5. Interactions with other medications and other forms of interactions

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 (subjective drowsiness and 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.

4.6. Pregnancy and breastfeeding

Pregnancy

Studies in animals did not shown any teratogenic effects. Taking into account to the lack of teratogenic effect in animal, no malformative effects are expected in human. Indeed to date, substances responsible for malformations in human have been shown to produce teratogenic effects in animals during well-conducted studies in two different animal species.

In clinical practice, the use of loperamide in the course of a limited number of pregnancies did not reveal any malformative or foetotoxic effect to date. Supplementary studies are nevertheless necessary to evaluate the consequences of exposure during pregnancy.

Consequently, the anticipated therapeutic benefits should be weighed against potential hazards and the use of loperamide should be considred during pregnancy only if necessary, especially during the first trimester.

If the treatment is prolonged, take account of its possible opiate-like properties, particularly on gastro-intestinal function in infants.

Breast-feeding

Allthough the quantity of loperamide which passes into breast milk is very low, small amounts of loperamide may appear in human breast milk. Consequently, breast-feeding is not recommended during treatment with loperamide.

If the treatment is prolonged, take into account its opiate-like properties.

Fertility

Reproduction studies in rats showed an impaired fertility in male and female at the loperamide dose of 40 mg/kg/day (see section 5.3).

4.7. Effects on the ability to drive vehicles and use machines

This medicine can cause drowsiness, dizziness or fatigue.

Therefore, it is advisable to use caution when driving a car or operating machinery..

4.8. Adverse effects

Adults and children aged ≥12 years

The safety of loperamide Hydrochloride was evaluated in 3076 adults and children aged ≥12 years who participated in 31 controlled and uncontrolled clinical trials of loperamide Hydrochloride used for the treatment of diarrhoea. Of these, 26 trials were in acute diarrhoea (N=2755) and 5 trials were in chronic diarrhoea (N=321).

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%).

In clinical trials in chronic diarrhoea, the most commonly reported (i.e., ≥1% incidence) ADRs were: flatulence (2.8%), constipation (2.2%), nausea (1.2%) and dizziness (1.2%).

The following table displays ADRs that have been reported with the use of loperamide Hydrochloride from either clinical trial (in acute or chronic diarrhoea or both) or post-marketing experience. The adverse effects within each system organ class, are ranked by frequency, using the following convention : Very common : <1/10 ; Common : <1/100, < 1/10 ; Uncommon : <1/ 1,000, < 1/100 ; Rare : <1/10,000, < 1/1,000 ; Very rare : <1/10,000 ; unknown (can not be estimated based on available data). The process of determination of postmarketing ADR does not distinguish the different indications (chronic or acute diarrhea) or populations (adults or children).

System Organ Class	Indesirable effects			
	Common	Uncommon	Rare	Unknown frequency
Nervous System Disorders	Headache[a] Dizziness[b]	Headache[b] Dizziness[a]		Drowsiness, Loss of consciousness, stupor, Depressed level of consciousness, hypertonia, coordination abnormalitiy
Gastrointestinal Disorders	Constipation, nausea, flatulence	Abdominal pain, abdominal discomfort, dry mouth	Abdominal distension[a]	Ileus (including Paralytic ileus), Megacolon (including Toxic megacolon), glossodynia, Acute pancreatitis
System Organ Class	Indesirable effects			
	Common	Uncommon	Rare	Unknown frequency

		Upper abdominal pain[a], vomiting[a] Dyspepsia[b]		
Skin and Subcutaneous Tissue Disorders		Rash[a]		Bullous eruption (including Stevens-Johnson syndrome, Toxic epidermal necrolysis and Erythema multiforme), Angioedema, Urticaria, Pruritus
Immune system disorder				Hypersensitivity reaction, Anaphylactic reaction (including Anaphylactic shock), and Anaphylactoid reaction.
Eye disorder				Miosis
Renal and Urinary Disorder				Urinary retention
General Disorders and Administration Site Conditions				Fatigue
a : acute diarrhea indication b : chronic diarrhea indication				

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 ADR 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 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: via the NAFDAC ADR eReporting form available on the Agency website, nafdac.gov.ng

4.9. Overdose

Symptoms:

In the event of overdose (including overdose linked to hepatic impairment), central nervous system depression (decrease in alertness, stupor, drowsiness, myosis, hypertonia, respiratory depression, motor incoordination), urinary retention and ileus may be observed. Children can be more sensitive to the effects on the central nervous system (CNS).

In individuals who have ingested overdoses of loperamide HCl, cardiac events such as QT interval and QRS complex prolongation as well as 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.

Emergency procedure, antidote:

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

If CNS symptoms of overdose occur, naloxone can be used as an antidote. Because the duration of action of loperamide is longer than that of naloxone (1 to 3 hours), it may be necessary to repeat administration of the latter. Consequently, the patient should be kept under medical supervision for at least 48 hours in order to detect any central nervous system depression

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic class : ANTIDIARRHEAL, ATC code: A07 DA 03

(A: Alimentary tract and metabolism)

- Antidiarrheal structural analog of opiates.
- Antisecretory activity by an increase in the hydroelectrolytic flow of the intestinal lumen towards the plasma pole of the enterocyst and reduction of the inverse flow.
- Slowing of colonic transit with an increase in segmentation contractions.
- Fast and lasting effect.
- Respects the bacteriological and parasitological characteristics of stools.

5.2. Pharmacokinetic properties

Loperamide is barely resorbed by the digestive tract. It is subject to a significant hepatic first pass effect.

The plasma concentrations are low (2 ng/ml after the administration of about 8 mg of loperamide per day).

In humans, the plasma peak is situated between 2 and 4 hours.

Loperamide is mainly metabolized by the liver and its elimination half-life is 10.8 hours with variations going from 9 to 14 hours. Studies on distribution in rats show a high affinity for the intestinal wall, loperamide binding preferably to the receptors of the longitudinal muscular layer. In humans, loperamide is readily absorbed by the intestine, but it is almost completely metabolized by the liver where it is conjugated and excreted by the bile. Due to the very large hepatic first pass effect, the plasma concentrations in loperamide remain very low. Its elimination is carried out mainly in the feces.

5.3. Preclinical safety data

Chronic repeat dose toxicity studies on loperamide of up to 12 months in the dog and 18 months in the rat have not shown any toxic effect other than some body weight reduction or gain and food consumption at daily doses of up to 5 mg/kg/day {8 times the maximal dose in human of 16 mg/day based on body surface area dose comparisons (mg/m2)} in dog and 40 mg/kg/day (20 times the maximal dose in human, based on body surface area dose comparisons (mg/m2)) in rat. The No Observed Adverse Effect Levels (NOAEL) in these studies were 0.3 mg/kg/day (~0.5 times the maximal dose in human based on body surface area dose comparisons (mg/m2)) and 2.5 mg/kg/day (~1.3 times the maximal dose in human based on body surface area dose comparisons (mg/m2)) in dogs and rats respectively.

Non-clinical in vitro and in vivo evaluation of loperamide hydrochloride 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.

Carcinogenicity and mutagenicity

There was no carcinogenic potential. Results of in vivo and in vitro genotoxicity studies indicated that loperamide is not genotoxic.

Reproductive Toxicology

Reproduction studies in rats, at very high doses of loperamide (40 mg/kg/day corresponding to 20 times the maximal dose in human, based on body surface area dose comparisons (mg/m2)), showed a maternal toxicity, impaired fertility in male and female and reduced fetal/pup survival. Lower doses (10 mg/kg, corresponding to 5 times the maximal dose in human, based on body surface area dose comparisons (mg/m2)) do not revealed any toxic effect in mother or fetus, and did not affect peri- and post-natal development.

6. PHARMACEUTICAL INFORMATION

6.1. List of excipients

Lactose monohydrate, corn starch, talc, magnesium stearate.

Composition of the capsule shell: gelatin, titanium dioxide, erythrosine, yellow ferric oxide, patent blue V, black ferrous oxide.

6.2. Incompatibilities

Not applicable.

6.3. Shelf Life

5 years.

6.4. Special precautions for storage

No special storage precautions.

6.5. Nature and content of the outer packaging

6,12 or 20 capsules in blister packs (PVC/Aluminum).

All presentations may not be marketed.

6.6. Special precautions for disposal and handling

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements. It also applies to administration device which should be disposed at the same time as the medicines and their packaging.

7. Marketing Authorisation Holder

Janssen Pharmaceutical N.V. Turnhoutseweg 30, B-2340 Beerse Belgium.

8. Drug Product Manufacturer

Lusomedicamenta Sociedade Technica Farmaceutica S.A. Estrada Consigilieri Pedroso 69 B Queluz De Baixo, 2730-055, Barcarene Portugal

9. NAFDAC REGISTRATION NUMBER

04-2941