SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

IMODIUM capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One capsule contains:
Active substance: Loperamide hydrochloride 2 mg.

Excipients with known effect
Lactose monohydrate 127 mg.

For the full list of the excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules.
White powder filled in capsules (size 4) with green cap and dark grey body.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

IMODIUM is indicated for control and symptomatic relief of acute diarrhea in adults and adolescents aged 12 years and older.

4.2 Posology and method of administration

Posology
Children above 12 years and Adults
The starting dose is 2 capsules (4 mg).
Continue treatment with 1 capsule (2 mg), after each loose (soft) stool.

The maximum daily dose is 8 capsules per day (16 mg).

Special populations

Peadiatric population
Imodium is Contraindicated in children less than 12 years of age.

Elderly
No dose adjustment is required in the elderly.

Renal impairment
No dose adjustment is required in patients with impaired renal function.

Hepatic impairment
Although no pharmacokinetic data are available in patients with hepatic impairment, loperamide HCl should be used with caution in these patients due to 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.

Attention: Do not use for more than 2 days. In all cases, discontinue treatment on the normalization of the feces, or if the patient has no further bowel movements for 12 hours, or in the event of constipation. In episodes of acute diarrhea, loperamide HCl is generally able to stop symptoms within 48 hours. If there are no appreciable results after this period, discontinue treatment and consult your doctor.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Children under the age of 12 years.
- in patients with acute dysentery characterized by blood in the stool and high fever;
- in patients with acute ulcerative colitis or pseudomembranous colitis due to the use of broad-spectrum antibiotics;
- in patients with bacterial enterocolitis caused by invasive organisms including Salmonella, Shigella and Campylobacter.

In general, the use of loperamide HCl is contraindicated in all cases in which inhibition of peristalsis should be initiated due to the possible risk of significant consequences such as ileus, megacolon and toxic megacolon. Imodium must be discontinued promptly when ileus, constipation or abdominal distension develop.

4.4 Special warnings and precautions for use

The treatment of diarrhea with loperamide HCl is only symptomatic. Whenever an underlying etiology can be determined, specific treatment should be given when appropriate. The priority in acute diarrhea 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 diarrhea. Use of this medicine does not preclude the administration of appropriate fluid and electrolyte replacement therapy.

Since persistent diarrhea can be an indicator of potentially more serious conditions, this medicine should not be used for prolonged periods until the underlying cause of the diarrhea has been investigated.

In acute diarrhea, if clinical improvement is not observed within 48 hours, the administration of Imodium should be discontinued and patients should be advised to consult their doctor.

Patients with AIDS treated with this medicine 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 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.

Cardiac events including QT interval and QRS complex prolongation and 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.

Caution is needed in patients with a history of drug abuse. Abuse and misuse of loperamide, has been described (see section 4.9). Loperamide is an opioid with low bioavailability and limited potential to penetrate the blood brain barrier at therapeutic doses. However, addiction is observed with opioids as a class.

4.5 Interaction with other medicinal products and other forms of interaction

Non-clinical data have demonstrated that loperamide is a substrate of P-glycoprotein.
Concomitant administration of loperamide (in a 16 mg single dose) with quinidine, or ritonavir (both P-glycoprotein inhibitors) showed two- to three-fold increases in plasma levels of loperamide.
The clinical relevance of this pharmacokinetic interaction with P-glycoprotein inhibitors when loperamide is given at the recommended doses (from 2 mg to a maximum of 16 mg per day) is unknown.

The concomitant administration of loperamide (in a 4 mg single dose) with itraconazole, a CYP3A4 and P-glycoprotein inhibitor, showed a three- to four-fold increase in plasma levels of loperamide. In the same study, gemfibrozil, a CYP2C8 inhibitor, showed a two-fold increase in plasma levels of loperamide. The combination of itraconazole and gemfibrozil showed a four-fold increase in peak plasma levels of loperamide and a thirteen-fold increase in total plasma exposure. These increases were not associated with effects on the central nervous system (CNS) as detected by psychomotor tests (e.g. subjective vertigo and the Digit Symbol Substitution Test).

The concomitant administration of loperamide (in a 16 mg single dose) with ketoconazole, a CYP3A4 and P-glycoprotein inhibitor, showed a five-fold increase in plasma levels of loperamide. This increase was not associated with increased pharmacodynamic effects as observed by pupillometry.

Concomitant treatment with oral desmopressin resulted in a three-fold increase in plasma concentrations of desmopressin, presumably due to slower gastrointestinal motility.

It is expected that drugs with similar pharmacological properties may potentiate the effect of Imodium, and that drugs that accelerate gastrointestinal transit may decrease its effect.

4.6 Fertility, pregnancy and lactation
Pregnancy
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 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.

Fertility
The effect on human fertility has not been evaluated.

4.7 Effects on ability to drive and use machines

Loss of consciousness, depressed level of consciousness, tiredness, dizziness, or drowsiness may occur when diarrhea is treated with this medicine. Therefore, it is advisable to exercise 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 HCl has been evaluated in 2755 adults and children aged ≥12 years who participated in 26 controlled and uncontrolled clinical trials with loperamide HCl used for the treatment of acute diarrhea.

The most commonly reported (i.e. with an incidence ≥1%) adverse drug reactions (ADRs) in clinical trials with loperamide HCl for the treatment of acute diarrhea were the following: constipation (2.7%), flatulence (1.7%), headache (1.2%) and nausea (1.1%).

Table 1 shows the ADRs reported with the use of loperamide HCl from either clinical trials (acute diarrhea) or post-marketing experience.

The frequency of the adverse reactions presented in Table 1 is defined according to 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)

Table 1: Adverse drug reactions

System Organ Class				
	Common	**Uncommon**	**Rare**	**Not known**
Immune System Disorders			Hypersensitivity reaction[a] Anaphylactic reaction (including Anaphylactic shock)[a] Anaphylactoid reaction[a]	
Nervous System Disorders	Headache	Dizziness Somnolence[a]	Loss of consciousness[a] Stupor[a], Depressed level of consciousness[a] Hypertonia[a] Coordination abnormality[a]	
Eye Disorders			Miosis[a]	
Gastrointestinal Disorders	Constipation Nausea Flatulence	Abdominal pain Abdominal discomfort Dry mouth Abdominal pain upper Vomiting Dyspepsia[a]	Ileus[a] (including paralytic ileus) Megacolon[a] (including toxic megacolon[b]) Abdominal distension	Acute pancreatitis
Skin and Subcutaneous Tissue Disorders		Rash	Bullous eruption[a] (including Stevens-Johnson syndrome, Toxic epidermal necrolysis and Erythema multiforme) Angioedema[a] Urticaria[a] 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).
b: See section 4.4 Special Warnings and Special Precautions for use.

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

4.9 Overdose

Symptoms
In the event of overdose ((including relative overdose due to hepatic dysfunction) CNS depression (stupor, coordination abnormality, somnolence, miosis, muscular hypertonia, 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, 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.
Upon cessation, cases of drug withdrawal syndrome have been observed in individuals abusing, misusing, or intentionally overdosing with excessively large doses of loperamide.

Treatment

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

If CNS 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 opioid receptors in the intestinal wall, 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 diarrhea receiving loperamide, onset of antidiarrheal action was observed within one hour following a single 4 mg dose. Clinical comparisons with other antidiarrheal 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 Ndemethylation 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.

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 – 20 times the maximum human use level (MHUL)), based on body surface area dose comparison (mg/m^2), loperamide impaired fertility and fetal survival in association with maternal toxicity in rats. Lower doses (≥ 10mg/kg/day – 5 times MHUL) revealed no effects on maternal or fetal 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

Lactose monohydrate, maize starch, talc, magnesium stearate, erythrosine, indigo carmine, iron oxide yellow, iron oxide black, titanium dioxide and gelatin.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

Box containing an opaque PVC/Al blister pack of 6, 10 or 12 capsules.

Not all pack sizes may be marketed

6.6 Special precautions for disposal

No special requirements.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. REGISTRATION HOLDER

Kenvue Hellas Commercial Single MemberS.A., Yakum, 6097200, Israel.

8. MANUFACTURER

JNTL Consumer Health (Belgium) BV, Antwerpen, Belgium.

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