SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

<Invented Name> 2 mg hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule, hard contains 2 mg of loperamide hydrochloride.

Excipient with known effect
Each capsule, hard contains 144.6 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard.

White opaque cap/White opaque body, size '4' hard gelatin capsule shells, imprinted with '2'on cap and 'L' on body with black ink filled with white to off-white power.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic treatment of acute diarrhoea in adults and children aged 12 years and over.

4.2 Posology and method of administration

Posology

Adults and children over 12 years of age:
Two capsules to be taken initially, followed by one capsule after each loose motion, up to a maximum of six capsules in any 24 hours.

Children under 12 years of age:
Not recommended

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.
This medicine must not be used for more than 2 days without medical advice and surveillance.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipient listed in section 6.1.

Loperamide should not be used as the primary therapy:

- In children less than 12 years of age.
- 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.
- In acute dysentery, characterized by blood in the stool and high fever
- When inhibition of gastro-intestinal peristalsis should be avoided such as in case of subileus, megacolon, toxic megacolon and certain intoxications.

4.4 Special warnings and precautions for use

Treatment of diarrhoea with loperamide is only symptomatic. Whenever an underlying etiology can be determined, specific treatment should be given when appropriate.

In patients with diarrhoea, especially in young children and elderly fluid and electrolyte depletions can occur. Administration of suitable fluid and electrolyte replacement therapy (ORS) is then the most important measure. A dry mouth can also be a sign of dehydration. In case of dehydration, a child may become dizzy and start vomiting. Then also administration of suitable fluids and electrolyte replacement therapy (ORS) is the most important measure.

If no clinical improvement is observed in acute diarrhea within 48 hours, Loperamide should be discontinued and the patient should be advised to consult his physician.

As soon as the stool becomes firmer or as soon as there is no stool for more than 12 hours occurred, the taking of loperamide should be discontinued.

Treatment with loperamide hydrochloride must be interrupted immediately when obstipation, abdominal distension or sub ileus develops.

When the recommended dose is exceeded, the chance of developing ileus is increased.

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

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. Loperamide hydrochloride should be used under medical supervision in patients with severe hepatic dysfunction.

Patients with AIDS treated with loperamide hydrochloride for diarrhoea should have therapy stopped at the earliest signs of abdominal distension. There have been isolated reports of toxic megacolon in AIDS patients with infectious colitis from both viral and bacterial pathogens treated with loperamide hydrochloride.

Since loperamide is not excreted in the urine, no dose adjustment is necessary for patients with renal impairment.

Loperamide hydrochloride should not be used in chronic diarrhoea, which requires follow-up by a physician.

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

Information about excipient:
<Invented Name> contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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 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 Fertility, Pregnancy and Lactation

Pregnancy
A limited amount of data from the use of loperamide in pregnant women is available. In one of two epidemiological studies the use of loperamide during early pregnancy suggested a possible moderate increased risk for hypospadia, however, an increased risk for major malformations could not be identified. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). 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.

If possible the use of loperamide should be avoided during the first trimester of pregnancy, however, it may be used during the second and third trimester of pregnancy

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
There are no data available on effects of loperamide hydrochloride on fertility in humans. Results of animal studies do not indicate any effect of loperamide hydrochloride on fertility at therapeutic doses.

4.7 Effects on ability to drive and use machines

Loperamide hydrochloride has moderate influence on the 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 hydrochloride.

Therefore, it is advisable to use caution when driving 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 hydrochoride used for the treatment of acute diarrhoea.

The most commonly reported (i.e. ≥1% incidence) adverse drug reactions (ADRs) in clinical trials with loperamide hydrochoride 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 hydrochoride 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] 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]) Glossodynia[a] Abdominal distension
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 hydrochoride. 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 hydrochoride (acute and chronic), including trials in children ≤ 12 years (N=3683).

b: See section 4.4 Special Warnings and Special Precautions for use.

Paediatric population

The safety of loperamide HCl was evaluated in 607 patients aged 10 days to 13 years of age who participated in 13 controlled or uncontrolled clinical studies using loperamide HCl in the treatment of acute diarrhea. Overall, the adverse reaction profile in this patient population was

similar to that observed in clinical studies with loperamide HCl in adults and children over 12 years of age.

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
After ingestion of an overdose, gastro-intestinal complaints may occur, consisting of nausea and vomiting, abdominal pain and abdominal cramps as well as a dry mouth.

In case of overdose (including relative overdose due to hepatic dysfunction), CNS depression (stupor, coordination abnormality, somnolence, miosis, muscular hypertonia, and respiratory depression), urinary retention and ileus may occur. Children may be more sensitive to CNS effects than adults.

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.

Treatment
In cases of overdose, ECG monitoring for QT interval prolongation should be initiated.
If symptoms of overdose occur, naloxone can be given as an antidote. If no effect occurs within 10 minutes, another cause must also be considered. 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.

For children, the naloxone dose is 0.01 mg/kg, with a maximum total dose of 10 mg. If no result is achieved, it is not a morphinomimetic effect.

In case of respiratory depression, ventilate if necessary. Other symptoms should be treated as such by an appropriate method.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Antipropulsives;
ATC code: A07DA03

Loperamide hydrochloride binds to the opiate receptor in the gut wall. Consequently, it inhibits the release of acetylcholine and prostaglandins, thereby reducing propulsive peristalsis, and increasing intestinal transit time. Loperamide increases the absorption of water

and electrolytes, especially in the ileum. This is done by increasing the NaCl co-transport or directly by blocking the calcium-dependent secretion. May also reduce gastrointestinal secretions, resulting in improvement in diarrhoea symptoms.

Loperamide increases the tone of the anal sphincter, which help reduce faecal incontinence and urgency. Onset of antidiarrhoeal effect occurred as soon as one hour after intake of a 4 mg dose of loperamide.

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
Loperamide hydrochloride is well 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 high affinity for the gut wall with preference for binding to the receptors in the longitudinal muscle layer. The plasma protein binding of loperamide is about 95 %, mainly to albumin. Non-clinical data have shown that loperamide is a P glycoprotein substrate.

Biotransformation
Loperamide is almost completely extracted and metabolised by the liver where it is 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 its high affinity for the gut wall and its high first pass metabolism, very little loperamide hydrochloride reaches the systemic circulation.

Elimination
The half-life of loperamide hydrochloride in man is about 11 hours with a range of 9 - 14 hours. Excretion takes place mainly via faeces.

Paediatric population

No pharmacokinetic studies were performed in the paediatric population. However, it is expected that pharmacokinetics and interactions with other drugs in this patient population are similar to those in adult patients.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

Acute and chronic studies on loperamide showed no specific toxicity.

Loperamide had no effect on fertility in male rats when administered orally prior to mating at doses up to approximately 40 mg/kg. No pregnancy occurred in females dosed with approximately 40 mg/kg. Lower doses (approximately 10 and 2.5mg/kg) did not affect female fertility. In rabbits no differences in pregnancy rate were observed when females were administered orally up to 40mg/kg.

No malformations of offspring were noted in rats and rabbits dosed up to 40 mg/kg. Loperamide did no show genotoxic potential.

In an 18-month carcinogenicity study in rats, with doses up to 100 times the maximum human dose no evidence of carcinogenesis was found.

Pre-clinical effects were only observed at exposures that exceed the maximum human exposure significantly suggesting minor clinical relevance.

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

Capsules content:
Lactose monohydrate
Maize Starch
Talc (E 553b)
Magnesium Stearate (E 470b)

Capsules shell:
Titanium Dioxide (E171)
Gelatin (E 441)

Printing Ink:
Shellac (E 904)
Black Iron Oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 30°C.
Store in the original container in order to protect from moisture.

6.5 Nature and contents of container

<Invented Name> hard capsules are available in clear PVC/Aluminium blisters pack.

Pack sizes:
Blister packs: 6, 10, 12, 20, 30, 60 and 200 hard capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

8 MARKETING AUTHORISATION NUMBER(S)

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT