Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Imodium 2 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 2 mg of loperamide hydrochloride.

Excipient with known effect - Each capsule contains 127 mg lactose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard. (capsule)

Gelatin capsules with an opaque green cap and an opaque dark grey body, containing white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults

As an adjunct in the management of acute diarrhoea, together with appropriate fluid and electrolyte replacement.

In the symptomatic control of diarrhoea associated with chronic inflammatory bowel disease, eg., Crohn's disease and ulcerative colitis, as an adjunct to specific measures such as corticosteroids and sulphasalazine. Use in these conditions should be under specialist supervision.

In the adjunctive short-term, control of post-surgical diarrhoea, including ileostomy.

Children

For the occasional use in the control of intractable diarrhoea under specialist supervision.

Since persistent diarrhoea can be an indicator of potentially serious conditions, the underlying cause must always be investigated.

4.2 Posology and method of administration

For oral administration. The capsules should be taken with water.

i) As an adjunct in the management of acute diarrhoea

Adults and children 9-12 years

1 to 2 capsules (2 to 4 mg) is the usual initial dose, followed by 1 capsule (2 mg) three times daily. The maximum daily dose should not exceed 10 mg.

Children 4-8 years

A total maximum daily dose of 4 mg in divided doses (see 4.4 Special warnings and precautions for use).

Under 4 years

Not recommended.

Use in 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, Imodium should be used with caution in such patients because of reduced first pass metabolism (see 4.4 Special warning and precautions for use).

ii) For the symptomatic treatment of diarrhoea associated with chronic bowel disorders

Adults only

Studies have shown that patients may need differing amounts of loperamide. The starting dosage should be between 4 to 8 mg (2 to 4 capsules) per day in divided doses depending on severity. If required, this dose can be adjusted according to response. Having established the patient's daily maintenance dose, the capsules may be administered on a twice daily regimen.

4.3 Contraindications

- Imodium is contraindicated in patients under 4 years of age
- Imodium is contraindicated in patients with a known hypersensitivity to loperamide hydrochloride or to any of the excipients
- Imodium should not be used as the primary therapy:

- In patients with acute dysentery, which is characterised by blood in the 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.

- Imodium should not be used when the inhibition of peristalsis is to be avoided due to the possible risk of significant sequelae including ileus, megacolon and toxic megacolon. Imodium must be discontinued promptly when constipation, abdominal distension or ileus develop.

4.4 Special warnings and precautions for use

Treatment of diarrhoea with loperamide HCl is only symptomatic. Whenever an underlying etiology can be determined, specific treatment should be given when appropriate.
The necessity for specific therapy, such as anti-infectives, should be borne in mind, particularly should treatment be required for a period longer than three days.

Loperamide should be used with caution when hepatic function, necessary for the drug's metabolism, is defective, as this may result in relative overdose leading to CNS toxicity.

Patients with AIDS treated with Imodium 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.

Antimotility agents such as loperamide may precipitate ileus and toxic megacolon in patients with ulcerative colitis, and should be avoided in severe acute attacks. It may be used cautiously in mild or less severe attacks as an adjunct to other measures, but should be discontinued promptly should abdominal distension or other untoward symptoms occur.

The stated dose should not be exceeded.

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.

Swallowing of capsules may be difficult for young children who should be carefully supervised to avoid any potential risk of choking.

If symptoms persist or get worse, or if new symptoms occur, patients should be advised to stop treatment and consult their physician.

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). If possible, the use of loperamide should be avoided during the first

trimester of pregnancy, however, if clinically necessary, the use of loperamide may be considered during the second and third trimester of pregnancy.

Breast-Feeding
Only very small amounts of loperamide hydrochloride may appear in human breast milk. Therefore, loperamide may be used during breast-feeding when dietary measures are insufficient and a drug-induced inhibition of intestinal motility is indicated.

Women who are pregnant or breast-feeding infants should 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

Tiredness, dizziness, or drowsiness may occur when diarrhoea is treated with Imodium. 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 HCl 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 HCl 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); very rare (<1/10,000); not known (cannot be estimated from the available data).

Table 1: Adverse Drug Reactions

System Organ Class	**Indication**			
	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		Rash	Bullous eruption[a] (including Stevens-Johnson syndrome, Toxic epidermal necrolysis and	

Tissue Disorders			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. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, website: www.hpra.ie.

4.9 Overdose

Signs and 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 paralytic 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 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 may be given as an antidote. Since the duration of action of loperamide is longer than that of naloxone 1 to 3 hrs), 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. Consequently, it inhibits the release of acetylcholine and prostaglandins, thereby 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, thereby reducing incontinence and urgency. Loperamide does not act centrally.

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 10.8 to 11 hours with a range of 9.1 to 14.4 hours. Excretion of the unchanged loperamide and the metabolites mainly occurs through the faeces.

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 and toxicity to reproduction and development.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
Lactose
Maize starch
Talc
Magnesium stearate

Capsule cap
Titanium dioxide (E171)
Yellow ferric oxide (E172)
Indigotindisulphonate sodium (E132)
Gelatin

Capsule body
Titanium dioxide (E171)
Black ferrous oxide (E172)
Indigotindisulphonate sodium (E132)
Erythrosin (E127)
Gelatin

6.2 Incompatibilities

Not applicable

6.3 Shelf life

5 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Imodium Capsules are packaged in blister packs consisting of polyvinylchloride, glass clear 250 micrometre and aluminium foil (thickness 20 micrometre) coating on the inner side with a colourless heat seal lacquer: PVC mixed polymers with acrylates 6 g/m^2, in an outer cardboard carton.

The packs contain 60 capsules.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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Tallaght
Dublin 24
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8 MARKETING AUTHORISATION NUMBER

PA23490/025/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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