Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Imodium Plus 2 mg/125 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient(s) with known effect
Each tablet contains less than 0.026 mg of benzyl alcohol and less than 4.4 mg of maltodextrin (which contains glucose).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet, uncoated.

White, capsule-shaped tablets debossed with "IMO" on one side, the other side is debossed with a line between "2" and "125".

The score line is not intended for breaking the tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Imodium Plus 2 mg/125 mg 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
Imodium Plus is contraindicated in children under 12 years (see section 4.3).

Use in the elderly
No dosage adjustments are required for the elderly.

Use in renal impairment
No dosage adjustment is necessary in patients with renal impairment.

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

Method of administration
Swallow the correct number of tablets whole with a drink of water.

4.3 Contraindications

- Children less than 12 years of age
- Hypersensitivity to the active substances or to 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

Imodium Plus must 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 Imodium Plus must be discontinued. Patients should be advised to consult their physician.

Patients with AIDS treated with Imodium Plus for diarrhoea should have therapy stopped at the earliest signs of abdominal distension. There have been isolated reports of obstipation with an increased risk of 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, Imodium Plus should be used with caution in such patients because of reduced first pass metabolism. This medicine 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. Imodium Plus should be used under medical supervision in patients with severe hepatic dysfunction.

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.

Imodium Plus contains benzyl alcohol, which may cause allergic reactions. Imodium Plus must be used with caution in patients with renal or hepatic impairment, or in patients who are pregnant or breast-feeding, because of the risk of accumulation and toxicity (metabolic acidosis).
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

This medicine contains less than 0.00044 mg of alcohol (ethanol) in each tablet. The small amount of alcohol in this medicine will not have any noticeable effects.

This medicine contains maltodextrin which contains glucose. Patients with rare 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 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 levels. 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. As these increases were not associated with measured central nervous system central nervous system (CNS) effects, as measured by psychomotor tests (i.e. subjective drowsiness and the Digit Symbol Substitutions 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.
Since simeticone is not absorbed from the gastrointestinal tract, no relevant interactions between simeticone and other drugs are expected.

Paediatric population
Interaction studies have only been performed in adults.

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 or simeticone possesses teratogenic or embryotoxic properties. Imodium Plus should not be given during pregnancy, especially during the first trimester, unless clinically justified.

Breast-feeding
Small amounts of loperamide may appear in human breast milk. Therefore Imodium Plus is not recommended during breast-feeding.

Fertility
The effect on human fertility has not been evaluated.

4.7 Effects on ability to drive and use machines

Imodium Plus has no or negligible influence on the ability to drive and use machines. However, tiredness, dizziness and drowsiness may occur in the setting of diarrheal syndromes treated with loperamide HCl (see section 4.8). Therefore, it is advisable to use caution when driving a car or operating machinery.

4.8 Undesirable effects

The safety of loperamide-simeticone was evaluated in 2040 patients who participated in five clinical trials. All trials were in patients with acute diarrhoea with gas related discomfort and with a chewable tablet loperamide-simeticone formulation. Four trials compared loperamide-simeticone with loperamide, simeticone and placebo and one trial compared two formulations of loperamide-simeticone with placebo.
The most commonly reported (i.e., ≥1% incidence) ADRs in clinical trials were (with % incidence): dysgeusia (2.6%) and nausea (1.6%).

The safety of loperamide HCl was evaluated in 2755 patients aged ≥ 12 years who participated in 26 controlled and uncontrolled clinical trials of loperamide HCl used for the treatment of acute diarrhoea. The most common ADRs (>1%) reported in these clinical trials were constipation (2.7%), flatulence (1.7%), headache (1.2%), and nausea (1.1%).

The safety of loperamide HCl was also evaluated in 321 patients who participated in 5 controlled and uncontrolled clinical trials of loperamide HCl used for the treatment of chronic diarrhoea. The most common ADRs (>1%) reported in these clinical trials were flatulence (2.8%), constipation (2.2%), dizziness (1.2%), and nausea (1.2%).

Paediatric population

The safety of loperamide HCl was evaluated in 607 patients aged 10 days to 13 years who participated in 13 controlled and uncontrolled clinical trials of loperamide HCl used for the treatment of acute diarrhoea. The only ADR reported for ≥ 1% of loperamide HCl-treated patients was vomiting.

Table 1 displays ADRs that have been reported with the use of loperamide-simeticone from either clinical trial or post-marketing experience. Additional ADRs reported with the use of loperamide HCl (one of the components of loperamide-simeticone) are also shown.

The frequency categories are based on clinical trial data with loperamide-simeticaon and loperamide HCl and 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	**Adverse events**			
	Frequency			
	Common	**Uncommon**	**Rare**	**Not known**
Immune system disorders			Hypersensitivity reaction[a], Anaphylactic reaction (including Anaphylactic shock)[a], Anaphylactoid reaction[a]	
Nervous system disorders	Headache[b], Dysgeusia	Somnolence[a], Dizziness[c]	Loss of consciousness[a], Depressed level of consciousness[a], Stupor[a], Hypertonia[a], Coordination abnormality[a]	
Eye disorders			Miosis[a]	
Gastrointestinal disorders	Nausea	Abdominal pain, Abdominal discomfort[b], Abdominal pain upper[b], Vomiting, Constipation, Abdominal distension[c], Dyspepsia[c], Flatulence, Dry mouth	Ileus[a] (including paralytic ileus), Megacolon[a] (including toxic megacolon[d])	Acute pancreatitis
Skin and subcutaneous tissue disorders		Rash	Bullous eruption (including Stevens-Johnson syndrome[a], Toxic epidermal necrolysis[a] and Erythema multiforme[a]), Angioedema[a], Urticaria[a], Pruritus[a]	
Renal and urinary disorders			Urinary retention[a]	
General disorders and administration site conditions		Asthenia	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 combined, including trials in children ≤ 12 years (N=3683).

[b] Inclusion of this term is based on ADRs reported in clinical trials with loperamide HCl. Frequency category assigned based on clinical trials with loperamide HCl in acute diarrhoea (N=2755).

[c] Inclusion of this term is based on post-marketing experience with loperamide-simeticone. Frequency category assigned based on clinical trials with loperamide-simeticone in acute diarrhoea (N = 618). Dizziness and abdominal distension were also identified as clinical trial ADRs with loperamide HCl.

[d] See section 4.4.

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

Symptoms
In case of overdosage (including relative overdosage 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, 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

If symptoms of overdosage 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.

Paediatric population
Children may be more sensitive to CNS effects than adults.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antipropulsive antidiarrheals, ATC code: A07D A53

Mechanism of Action

Loperamide HCl
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. Imodium Plus does not act centrally.

Simeticone
Simeticone is an inert surface-active agent with anti-foaming properties thereby potentially relieving gas-related symptoms associated with diarrhoea.

Simeticone is liquid dimethicone activated with finely divided silicon dioxide to enhance the defoaming properties of the silicone.

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 metabolised, 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 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, based on body surface area) 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

Calcium hydrogen phosphate
Microcrystalline cellulose
Acesulfame potassium
Artificial vanilla flavour (includes propylene glycol, maltodextrin, ethanol and benzyl alcohol)
Sodium starch glycolate (Type A)
Stearic acid.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 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 polychlorotrifluoroethylene/PVC film, heat seal coating and aluminium foil.

or

Bend and peel blisters comprising polychlorotrifluoroethylene/PVC film, heat seal coating, aluminium foil/PET/paper.

Blister strips of 2, 4, 5, or 6 tablets in pack sizes of 6, 8, 10, 12, 15, 16, 18 and 20 tablets packed in printed cardboard cartons.

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

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High Street
Tallaght
Dublin 24
D24 YK8N
Ireland

8 MARKETING AUTHORISATION NUMBER

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