Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Imodium Plus 2mg/125mg Chewable Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each chewable tablet contains loperamide hydrochloride 2 mg and simeticone equivalent to 125 mg dimeticone.
Excipients: include 300 mg sorbitol (E420) and approximately 50 mg sucrose.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Chewable tablet.
Whhite, round, flat-faced tablets wiht a vanilla-mint odour debossed with "IMO" on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Imodium Plus is 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

Adults over 18 years:
Chew 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:
Chew 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.

Use in children:
Imodium Plus must not be used in children under 12 years.

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

Renal impairment:
No dosage adjustment is necessary in renal impairment.

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 4.4 Special warnings and special precautions for use).

4.3 Contraindications

Imodium Plus must not be used in:

- Children less than 12 years of age
- Patients with a known hypersensitivity (allergy) to loperamide hydrochloride, simeticone or of the excipients.
- Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency, because the product contains sorbitol and sucrose
- 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 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. 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

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 (ie.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.

4.6 Fertility, pregnancy and lactation

Use in 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.

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

4.7 Effects on ability to drive and use machines

Tiredness, dizziness and drowsiness have been reported in patients taking loperamide. If affected, patients should not drive or operate machinery. See Section 4.8 Undesirable effects.

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%).

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-simeticone 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); and very rare (<1/10,000).

System Organ Class	Adverse events		
	Frequency		
	Common	**Uncommon**	**Rare**
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])
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-,arketing ADRs did not differentiate between chronic and acute indication sor adults and children the frequency 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 Special Warnings and Special Precautions for use.

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

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antipropulsive antidiarrheals, ATC code: A07D A53

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

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.

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 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 reproductive toxicity studies in rats, very high doses of loperamide, associated with maternal toxicity, impaired fertility and foetal survival. Lower doses had no effects on maternal or foetal health and did not affect peri- and post-natal development.

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

Sucrose and corn starch
Microcrystalline cellulose
Basic butylated methacrylate copolymer

Cellulose acetate
Sorbitol (E420)
Dextrates
Natural and artificial vanilla mint flavour (including sucrose, maltodextrin, modified corn starch, corn syrup solids, polyglycerol ester of fatty acids, calcium phosphate, enzyme modified milk powder)
Saccharin sodium
Stearic acid
Calcium phosphate.

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

Chewable tablets are packed in non child resistant push through blisters. The blister consists of: ACLAR/PVC film, aluminium foil and heat seal coating. The heat seal coating contains vinyl and acrylic.

Blister strips of 2, 4, 5, or 6 tablets in pack sizes of 2, 4, 5, 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 of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

McNeil Healthcare (Ireland) Ltd
Airton Road
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8 MARKETING AUTHORISATION NUMBER

PA 0823/060/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 August 1998
Date of last renewal: 01 September 2007

10 DATE OF REVISION OF THE TEXT

May 2013