SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Imodium Instants

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Loperamide hydrochloride 2 mg per tablet.

Excipients with known effect: Each tablet contains 0.750 mg of Aspartame (E951) which is equivalent to 0.055 mg/mg and Mint flavour, which contains less than 0.00066mg of benzyl alcohol, less than 0.24 mg of maltodextrin (which contains glucose) and traces of sulphites.

For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Orodispersible Tablet
Imodium Instants are white to off-white, circular, freeze-dried tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the symptomatic treatment of acute diarrhoea in adults and children aged 12 years and over.

For the symptomatic treatment of acute episodes of diarrhoea associated with Irritable Bowel Syndrome in adults aged 18 years and over following initial diagnosis by a doctor.

4.2 Posology and method of administration

The orodispersible tablet should be placed on the tongue, The tablet will dissolve and is to be swallowed with saliva. No liquid intake is needed for the orodispersible tablet.

Acute diarrhoea:
Adults, the elderly, and children 12 years and over:
Two tablets (4 mg) initially followed by 1 tablet (2 mg) after every loose stool. The maximum daily dose should not exceed 6 tablets (12 mg).

Symptomatic treatment of acute episodes of diarrhoea associated with irritable bowel syndrome
Adults aged 18 years and over:
Two tablets (4 mg) initially, followed by 1 tablet (2 mg) after every loose stool, or as previously advised by your doctor. The maximum daily dose should not exceed 6 tablets (12 mg).

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 Instants should be used with caution in such patients because of reduced first pass metabolism. (see 4.4 Special warnings and special precautions for use).

Method of administration:
Oral use. Allow the tablet to disintegrate on the tongue and swallow the medication.

4.3 Contraindications

Imodium Instants is contraindicated:

- in patients with a known hypersensitivity to loperamide hydrochloride or to any of the excipients.
- in children less than 12 years of age.
- in patients with acute dysentery, which is characterised by blood in 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 Instants 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. Imodium Instants must be discontinued promptly when ileus, constipation or abdominal distension develop.

4.4 Special warnings and precautions for use

Treatment of diarrhoea with Imodium Instants is only symptomatic. Whenever an underlying etiology can be determined, specific treatment should be given when appropriate. The priority in acute diarrhoea 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 diarrhoea. Use of Imodium Instants does not preclude the administration of appropriate fluid and electrolyte replacement therapy.

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

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

Patients with AIDS treated with Imodium Instants for diarrhoea 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, Imodium Instants 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.

If patients are taking this medicine to control episodes of diarrhoea associated with Irritable Bowel Syndrome previously diagnosed by their doctor, and clinical improvement is not observed within 48 hours, the administration of loperamide HCl should be discontinued and they should consult with their doctor. Patients should also return to their doctor if the pattern of their symptoms changes or if the repeated episodes of diarrhoea continue for more than two weeks.

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.

Special Warnings to be included on the leaflet:

Only take Imodium Instants to treat acute episodes of diarrhoea associated with Irritable Bowel Syndrome if your doctor has previously diagnosed IBS.

If any of the following now apply, do not use the product without first consulting your doctor, even if you know you have IBS:

- If you are aged 40 or over and it is some time since your last IBS attack
- If you are aged 40 or over and your IBS symptoms are different this time
- If you have recently passed blood from the bowel
- If you suffer from severe constipation
- If you are feeling sick or vomiting
- If you have lost your appetite or lost weight
- If you have difficulty or pain passing urine
- If you have a fever
- If you have recently travelled abroad

Consult your doctor if you develop new symptoms, if your symptoms worsen, or your symptoms have not improved over two weeks.

Sulphites can cause allergy like reactions, most commonly asthma symptoms in those with underlying asthma. Allergic rhinitis like reactions, urticaria and anaphylaxis might be observed.

This medicine contains maltodextrin which contains glucose. Patients with rare glucose-galactose malabsorption should not take this medicine.

Imodium Instants contains benzyl alcohol, which may cause allergic reactions. Imodium Instants 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).

Neither non-clinical nor clinical data are available to assess aspartame use in infants below 12 weeks of age.

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

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 loperamide in pregnancy, especially during the first trimester.

Breast-Feeding

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

Women who are pregnant or breast-feeding 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 diarrhoea is treated with loperamide. 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]) Glossodynia[a] 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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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 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 the opiate receptor in the 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 diarrhoea receiving loperamide, onset of anti-diarrhoeal action was observed within one hour following a single 4 mg dose. Clinical comparisons with other anti-diarrhoeal 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 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

Preclinical data reveal no hazard for humans based on conventional studies of single and repeated dose toxicity, genotoxicity, carcinogenicity and toxicity to reproduction and development.

5.3.1 GENERAL TOXICOLOGY

Loperamide show low acute toxicity. Chronic toxicity studies suggest NOAELs ranging from 0.3 to 10 mg/kg with no adverse effects except reduction in body weight gain at doses higher than the Maximum Human Use Level.

5.3.2 GENETIC TOXICOLOGY

Loperamide is non mutagenic in in vitro and in vivo assays.

5.3.3 CARCINOGENICITY

There is no preclinical data available. However, loperamide is considered noncarcinogenic due to its non-mutagenic potential and no carcinogenic effects or abnormalities reported in the chronic oral studies conducted in rats up to 40 mg/kg and 6, 12 and 18 months of treatment.

5.3.4 TERATOGENICITY

In reproduction and developmental studies, loperamide had no effects on peri- and post-natal development up to the dose of 20 mg/kg/day.

5.3.5 FERTILITY

Loperamide has no adverse effect on fertility in male rats up to 40mg/kg. In female rats 10 mg/kg was reported with no adverse effects on fertility.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Gelatin
Mannitol
Aspartame
Sodium hydrogen carbonate
Mint flavour (contains maltodextrin (which contains glucose), benzyl alcohol and traces of sulphites)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store in the original package

6.5 Nature and contents of container

All-aluminium blister packs of 2, 3, 4 or 6 tablets in printed cardboard cartons. The all-aluminium blisters are made from paper, PET, aluminium, PVC and polyamide.

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 MARKETING AUTHORISATION HOLDER

McNeil Products Limited
50-100 Holmers Farm Way
High Wycombe
Buckinghamshire
HP12 4EG
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 15513/0345

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20 May 2002

10 DATE OF REVISION OF THE TEXT

21/04/2026