

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Imodium Instants 2 mg Orodispersible Tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Loperamide hydrochloride 2 mg per tablet.

Excipient with known effect - Each tablet contains 0.750 mg of Aspartame (E951) which is equivalent to 0.055 mg/mg and it contains Mint flavour which contains less than 0.00066 mg of benzyl alcohol. The Mint flavouring contains traces of Sulphites.

For a full list of excipients see section 6.1.

## 3 PHARMACEUTICAL FORM

Orodispersible tablet.

White to off-white, circular, freeze-dried tablets.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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

### 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.

#### Adults and children over 12 years only

The usual dose is 2 tablets initially, followed by 1 tablet after each further episode of diarrhoea up to a maximum of 5 in 24 hours.

#### 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 precautions for use).

#### Method of administration

Oral.

### 4.3 Contraindications

- Imodium use is contraindicated in patients under 12 years of age.

- Imodium Instants are 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.

Imodium is not a substitute for rehydration therapy. In addition to taking Imodium, the patient should be advised to drink plenty of fluids such as water, clear soup and squash.

Patients should be advised to consult their doctor if diarrhoea persists for more than 24 hours.

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 Instants 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.

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.

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

The package leaflet contains the following information:

- This medicine contains 0.750 mg of Aspartame (E951) which is equivalent to 0.055 mg/mg.

Aspartame (E951) is a source of phenylalanine. It may be harmful if you have phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.

- Imodium Instants contains Mint flavour, which contains less than 0.00066 mg of benzyl alcohol. Benzyl alcohol 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).

- Mint flavour contains traces of sulphites. This may rarely cause severe hypersensitivity reactions and bronchospasm.
- This medicine contains less than 0.00003 mg of alcohol (ethanol) in each tablet. The small amount of alcohol in this medicine will not have any noticeable effects.
- This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

#### **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

The safety of loperamide in human pregnancy has not been established.

##### 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 infants 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**

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  $\geq 12$  years

The safety of loperamide HCl was evaluated in 2755 adults and children aged  $\geq 12$  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.  $\geq 1\%$  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 ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  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
<b>Immune System Disorders</b>			Hypersensitivity reaction <sup>a</sup> Anaphylactic reaction (including Anaphylactic shock) <sup>a</sup> Anaphylactoid reaction <sup>a</sup>	
<b>Nervous System Disorders</b>	Headache	Dizziness Somnolence <sup>a</sup>	Loss of consciousness <sup>a</sup> Stupor <sup>a</sup> Depressed level of consciousness <sup>a</sup> Hypertonia <sup>a</sup> Coordination abnormality <sup>a</sup>	
<b>Eye Disorders</b>			Miosis <sup>a</sup>	
<b>Gastrointestinal Disorders</b>	Constipation Nausea Flatulence	Abdominal pain Abdominal discomfort Dry mouth Abdominal pain upper Vomiting Dyspepsia <sup>a</sup>	Ileus <sup>a</sup> (including paralytic ileus) Megacolon <sup>a</sup> (including toxic megacolon <sup>b</sup> ) Abdominal distension Glossodynia	Acute pancreatitis
<b>Skin and Subcutaneous Tissue Disorders</b>		Rash	Bullous eruption <sup>a</sup> (including Stevens-Johnson syndrome, Toxic epidermal necrolysis and Erythema multiforme) Angioedema <sup>a</sup> Urticaria <sup>a</sup> Pruritus <sup>a</sup>	
<b>Renal and Urinary Disorders</b>			Urinary retention <sup>a</sup>	
<b>General Disorders and Administration Site Conditions</b>			Fatigue <sup>a</sup>	

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  $\leq 12$  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](http://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 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 hours), the patient should be kept under constant observation for at least 48 hours in order to detect any possible depression of the central nervous system.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Antipropulsives, ATC code: A07DA03

Loperamide binds to the opiate receptors in the gut wall, reducing propulsive peristalsis and increasing intestinal transit time. Loperamide increases the tone of the anal sphincter.

In a double blind randomised clinical trial in 56 patients with acute diarrhoea receiving loperamide, onset of antidiarrhoeal action was observed within one hour following a single 4mg dose. Clinical comparisons with other antidiarrhoeal 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

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 Warnings and Precautions), loperamide has cardiac electrophysiological actions consisting of inhibition of potassium (hERG) and sodium currents, and arrhythmias.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Gelatin  
Mannitol (E421)  
Aspartame (E951)  
Sodium hydrogen carbonate  
Mint flavour

## **6.2 Incompatibilities**

Not applicable.

## **6.3 Shelf life**

4 years.

## **6.4 Special precautions for storage**

This medicine does not require any special storage conditions.

## **6.5 Nature and contents of container**

All-aluminium blister packs of 6, 12, 18, and 24 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 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**

Johnson & Johnson (Ireland) Limited  
Airton Road  
Tallaght  
Dublin 24  
Ireland

## **8 MARKETING AUTHORISATION NUMBER**

PA0330/045/001

## **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 03 October 2003

Date of last renewal: 03 October 2008

## **10 DATE OF REVISION OF THE TEXT**

April 2023