Professional information for IMODIUM® MELT TABLETS

SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

IMODIUM® MELT 2 mg TABLETS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 mg loperamide hydrochloride.

Excipients with known effect:

Contains sweetener: Each tablet contains 0,75 mg aspartame (E951).

Contains mannitol (E421).

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Orodispersible tablets.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults and children 6 years and older

IMODIUM® MELT TABLETS are indicated for the control and symptomatic relief of acute and chronic non-specific diarrhoea and inhibit peristalsis and slow intestinal transit time in patients with ileostomies, colostomies and other intestinal resections.

4.2 Posology and method of administration

Posology

IMODIUM® MELT TABLETS should not be used in children under 6 years of age.

Acute non-specific diarrhoea

Adults: 2 tablets as an initial dose followed by 1 tablet after each subsequent loose stool.

Children (6 – 12 years): 1 tablet as an initial dose followed by 1 tablet after each subsequent loose stool.

Do not exceed the following maximum daily dosages.

WEIGHT IN KILOGRAMS (kg)	MAXIMUM DAILY DOSE
from 14 kg	2 tablets (4 mg)
from 20 kg	3 tablets (6 mg)
from 27 kg	4 tablets (8 mg)
from 34 kg	5 tablets (10 mg)
from 40 kg	6 tablets (12 mg)
from 47 kg	7 tablets (14 mg)
from 54 kg	8 tablets (16 mg)

Important: Stop IMODIUM® MELT TABLETS as soon as diarrhoea is under control.

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

Chronic non-specific diarrhoea (consult your doctor)

With individually adjusted dosage it is usually possible to obtain a virtually normal bowel movement.

The initial dose is 2 fast-dissolving tablets (4 mg) daily for adults and 1 tablet (2 mg) daily for children of 6 years and over.

The initial dose should be adjusted until 1 – 2 solid stools per day are obtained. This is usually achieved on a maintenance dose of 1 – 6 tablets (2 – 12 mg) daily.

If constipation occurs, the dosage should be decreased.

Special populations

Elderly

No dose adjustment is required for the elderly.

Renal impairment

No dose adjustment is required for patients with renal impairment.

Hepatic impairment

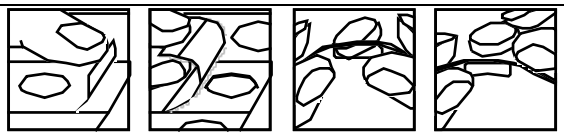
Although no pharmacokinetic data are available in patients with hepatic impairment, IMODIUM® MELT TABLETS should be used with caution in such patients because of reduced first pass metabolism (see section 4.4 below).

Method of administration

Instructions for use/handling:

To take the tablets out of the blister:

- pull the edge of the foil,
- tear the foil completely off,
- press out the tablet, remove the tablet.



Since the fast-dissolving tablets are fragile, the tablets should not be pushed through the blister as this would damage them.

The IMODIUM® MELT TABLETS tablet should be placed on the tongue.

The orodispersible tablet will dissolve and is to be swallowed with saliva. No fluid intake is needed.

4.3 Contraindications

- IMODIUM® MELT TABLETS are contraindicated in patients with a known hypersensitivity to loperamide hydrochloride or to any of the other ingredients in IMODIUM® MELT TABLETS (see section 6.1).
- IMODIUM® MELT TABLETS are contraindicated in children under 6 years of age.
- IMODIUM® MELT TABLETS should not be used as the primary therapy in patients with acute dysentery, which is characterised by blood in stools and high fever.
- IMODIUM® MELT TABLETS should not be used:
    - 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.

In general, IMODIUM® MELT TABLETS 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. IMODIUM® MELT TABLETS must be discontinued promptly when constipation, abdominal distension or ileus develop.

4.4 Special warnings and precautions for use

Treatment of diarrhoea with IMODIUM® MELT TABLETS is only symptomatic. Whenever an underlying aetiology can be determined, specific treatment should be given when appropriate (or when indicated).

In patients with diarrhoea, especially in infants, fluid and electrolyte depletion may occur. In such cases administration of appropriate fluid and electrolyte replacement (oral rehydration therapy (ORT)) is the most important measure. IMODIUM® MELT TABLETS should not be given to children under 6 years of age without medical prescription and supervision. IMODIUM® MELT TABLETS is not recommended for routine use in acute or chronic diarrhoea in children under the age of 6 years (see section 4.3).

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

Patients with acquired immunodeficiency syndrome (AIDS) treated with IMODIUM® MELT TABLETS for diarrhoea should have therapy stopped at the earliest signs of abdominal distension. There have been reports of obstipation with an increased risk for toxic megacolon in AIDS patients with infectious colitis from both viral and bacterial pathogens treated with IMODIUM® MELT TABLETS.

Although no pharmacokinetic data are available in patients with hepatic impairment, IMODIUM® MELT TABLETS should be used with caution in such patients because of reduced first pass metabolism.

IMODIUM® MELT TABLETS 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.

Abuse and misuse of loperamide, as an opioid substitute, have been described in individuals with opioid addiction (see section 4.9). 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® MELT TABLETS contains aspartame. Aspartame is hydrolysed in the gastrointestinal tract when orally ingested. One of the major hydrolysis products is phenylalanine.

4.5 Interaction with other medicines and other forms of interaction

Non-clinical data have shown that loperamide is a *P*-glycoprotein substrate. In two separate studies, 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 with concomitant administration with quinidine, but not with ritonavir; there was evidence of respiratory suppression. The clinical relevance of this pharmacokinetic interaction with *P*-glycoprotein inhibitors, when loperamide is given at recommended dosages (2 mg, up to 16 mg maximum daily dose), 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 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 medicines with similar pharmacological properties may potentiate loperamide's effect and that medicines that accelerate gastrointestinal transit may decrease its effect.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of use during pregnancy has not been established.

Breastfeeding

Small amounts of loperamide may appear in human breast milk.

Therefore, IMODIUM® MELT TABLETS is not recommended during breastfeeding.

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 in the setting of diarrhoeal syndromes treated with IMODIUM® MELT TABLETS. Therefore, it is advisable to use caution when driving a car or operating machinery (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions in patients with acute diarrhoea are constipation, flatulence, headache and nausea (adults and children 12 years and older) and vomiting (children under 12 years).

The most commonly reported adverse reactions in adults and children 12 years and older with chronic diarrhoea are dizziness, headache, flatulence, constipation and nausea.

Adverse events in patients with acute diarrhoea

Nervous system disorders:

Frequent: headache

Less frequent: dizziness

Gastrointestinal disorders:

Frequent: constipation, dry mouth, flatulence, abdominal cramp, colic, nausea

Less frequent: abdominal pain, vomiting, abdominal discomfort, upper abdominal pain, abdominal distension

Skin and subcutaneous tissue disorders:

Less frequent: rash

Adverse events in patients with chronic diarrhoea

Nervous system disorders:

Frequent: dizziness, headache

Gastrointestinal disorders:

Frequent: constipation, nausea, vomiting, meteorism, abdominal pain, abdominal cramp, colic, flatulence

Less frequent: dry mouth, abdominal discomfort, dyspepsia

Adverse events in patients with acute or chronic diarrhoea

Gastrointestinal disorders:

Frequent: nausea, constipation, abdominal cramp

Adverse event in paediatric patients (under 12 years) with acute diarrhoea

Nervous system disorders:

Less frequent: somnolence, dizziness, headache

Gastrointestinal disorders:

Frequent: vomiting

Less frequent: nausea, abdominal pain, constipation

Skin and subcutaneous tissue disorders:

Less frequent: rash

Post-marketing experience

Immune system disorders:

Less frequent: allergic reactions, hypersensitivity reactions including anaphylactic shock and anaphylactoid reactions

Psychiatric disorders:

Less frequent: drowsiness

Nervous system disorders:

Less frequent: abnormal coordination, depressed level of consciousness, hypertonia, loss of consciousness, somnolence, stupor

Eye disorders:

Less frequent: miosis

Gastrointestinal disorders:

Less frequent: ileus (including paralytic ileus), megacolon including toxic megacolon, glossodynia, abdominal distension

Skin and subcutaneous tissue disorders:

Less frequent: urticaria, pruritus, angioedema, and bullous eruptions, including Stevens-Johnson Syndrome, erythema multiforme and toxic epidermal necrolysis

Renal and urinary disorders:

Less frequent: urinary retention

General disorders and administration site disorders:

Less frequent: fatigue.

A number of the adverse events reported during the clinical investigations and post-marketing experience with IMODIUM® MELT TABLETS are also frequent symptoms of the underlying diarrhoeal syndrome (abdominal pain/discomfort, nausea, vomiting, dry mouth, tiredness, drowsiness, dizziness, constipation, and flatulence). These symptoms may be difficult to distinguish from undesirable medicine effects.

With IMODIUM® MELT TABLETS, a burning or prickling sensation on the tongue immediately following its use may occur. An increased risk of abdominal pain, including pancreatitis has been reported.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of IMODIUM® MELT TABLETS is important. It allows continued monitoring of the benefit/risk balance of IMODIUM® MELT TABLETS. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

For further information, please contact the Johnson & Johnson call centre on 0860 410032 (landline).

4.9 Overdose

Signs and symptoms:

In case of overdose (including relative overdose due to hepatic dysfunction), central nervous system depression (e.g. stupor, coordination abnormality, somnolence, miosis, muscular hypertonia and respiratory depression), urinary retention, constipation and paralytic ileus may occur. Children may be more sensitive to central nervous system effects of loperamide than adults. Convulsions have been reported in children under the age of 2 years. See section 4.3. Excessive inhibition of peristalsis with nausea and dryness of the mouth.

In individuals who have intentionally ingested of loperamide HCl, QT interval and QRS complex prolongation and/or serious ventricular dysrhythmias, including Torsade de Pointes, have been observed (see section 4.4). Fatal cases have also been reported. Abuse, misuse and/or overdose with excessively large doses of loperamide, may unmask 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:

Treatment is symptomatic and supportive. A slurry of activated charcoal given within 3 hours after ingestion of IMODIUM® MELT TABLETS is likely to decrease absorption. If symptoms of overdose occur, naloxone can be given as an antidote. Since the duration of action of IMODIUM® MELT TABLETS 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 central nervous system depression.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A.11.9 Anti-diarrhoeals.

Pharmacotherapeutic group: Antipropulsives.

ATC code: A07 DA03.

Loperamide hydrochloride inhibits hypermotility by direct action on the bowel wall. Excessive propulsion of the intestinal contents is reduced by way of myenteric receptors which control smooth muscle activity. Excessive fluid loss may be reduced indirectly by mucosal relaxation.

Loperamide hydrochloride normalises the stool in both acute and chronic 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 %.

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 medicine remain extremely low.

Excretion:

The half-life of loperamide is about 11 hours with a range of 9 – 14 hours. Excretion of the unchanged loperamide and the metabolites mainly occurs through the faeces.

Special populations:

Paediatrics:

No pharmacokinetic studies were performed in the paediatric population. It is expected that pharmacokinetic behaviour of loperamide and interactions with loperamide will be similar to those in adults.

5.3 Preclinical safety data

No further information of relevance available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Aspartame (E951),

gelatine,

mannitol (E421),

mint flavour,

sodium hydrogen carbonate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Store at or below 25℃.

Protect from moisture.

6.5 Nature and contents of container

Carton containing one aluminium blister with 6 or 10 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Johnson & Johnson (Pty) Ltd.

241 Main Road

Retreat

7945

South Africa

8. REGISTRATION NUMBER

29/11.9/0213

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

04 March 2005

10. DATE OF REVISION OF THE TEXT

To be allocated by SAHPRA.