Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Loperamide Clonmel 2 mg orodispersible tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 mg loperamide hydrochloride.

Excipient with known effect
Each tablet contains 3 mg aspartame.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Orodispersible tablet.

Loperamide Clonmel are white to off-white, circular, flat face, bevelled edge, uncoated orodispersible tablets, plain on both sides with a diameter of 7 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For symptomatic treatment of acute diarrhoea in adolescents from 12 years of age and adults, unless causative treatment is available.

Treatment with loperamide hydrochloride for more than 2 days may only be carried out under medical advice and follow-up monitoring.

4.2 Posology and method of administration

Posology

Adults
Two orodispersible tablets (equivalent to 4 mg of loperamide hydrochloride) as initial dose for treatment of acute diarrhoea followed by one 1 orodispersible tablet (equivalent to 2 mg of loperamide hydrochloride) after every subsequent loose stool.

A daily dose of 6 orodispersible tablets (equivalent to 12 mg of loperamide hydrochloride) must not be exceeded.

Paediatric population

Adolescents from 12 years of age
One orodispersible tablet (equivalent to 2 mg of loperamide hydrochloride) at the beginning of treatment of acute diarrhoea and after every subsequent loose stool.

A daily dose of 4 orodispersible tablets (equivalent to 8 mg of loperamide hydrochloride) must not be exceeded.

Children under 12 years
Loperamide Clonmel is not suitable for children below 12 years of age due to the high content of active substance. For this purpose other preparations are available on medical prescription.

Special populations

Renal impairment
As the majority of the active substance is metabolised and the metabolites or the unchanged active substance are excreted with the faeces, no dose adjustment is necessary in patients with renal impairment.

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

Method of administration
Loperamide Clonmel is placed on the tongue. The orodispersible tablet disintegrates immediately on the tongue and is swallowed with the saliva. No further fluid intake is required.

The duration of treatment with Loperamide Clonmel is limited to 2 days.
If diarrhoea persists after two days of treatment with Loperamide Clonmel, the patient is advised to see a doctor. If necessary, further diagnostic measures can be considered.

Note
For this pharmacy-only medicine, patients are told in the package leaflet not to exceed the recommended dosage and duration of use of 2 days, as severe constipation may occur.

Treatment with loperamide hydrochloride for more than 2 days may only be administered following medical advice and follow-up monitoring.

4.3 Contraindications

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- children less than 12 years of age. (Children less than 2 years of age must not be treated with loperamide. Children between 2 and 12 years of age must be treated with loperamide only after medical prescription)
- conditions in which an inhibition of peristalsis is to be avoided due to possible risks of sequelae including ileus, megacolon and toxic megacolon. Loperamide hydrochloride must be discontinued promptly when constipation, abdominal distension or ileus develop.
- diarrhoea associated with fever and/or blood in stools
- diarrhoea occurring during or after use of antibiotics (pseudomembranous [antibiotic-associated] colitis)
- bacterial intestinal inflammation caused by pathogens invading the intestinal wall (e.g. Salmonella, Shigella, and Campylobacter)
- chronic diarrhoea. (Chronic diarrhoea must only be treated with loperamide hydrochloride following medical prescription.)
- acute exacerbation of ulcerative colitis

Loperamide should only be taken after medical advice if liver disease is present or persisted because the breakdown of loperamide may be delayed in severe hepatic impairment.

4.4 Special warnings and precautions for use

Treatment of diarrhoea with loperamide hydrochloride is symptomatic only. Whenever an underlying aetiology can be determined, the cause should be treated if possible.

Diarrhoea can lead to large losses of fluid and electrolytes. Therefore, the most important therapeutic measure for diarrhoea is to replace the fluid and electrolytes. This is particularly important in children.

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

Patients with AIDS treated with loperamide hydrochloride 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, loperamide hydrochloride should be used with caution in such patients because of reduced first pass metabolism. Patients with liver dysfunction should be closely monitored for signs of CNS toxicity.

In individuals with opioid dependence, abuse and misuse of loperamide for opioid substitution have been reported (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.

Excipients
Contains aspartame which is a source of phenylalanine and may be harmful for patients with phenylketonuria.

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 concentration 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 the effect of loperamide and that drugs that accelerate gastrointestinal transit may decrease its effect.

4.6 Fertility, pregnancy and lactation

Pregnancy
A limited amount of data from the use of loperamide in pregnant women is available. In one of two epidemiological studies the use of loperamide during early pregnancy suggested a possible moderate increased risk for hypospadia, however, an increased risk for major malformations could not be identified. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

If possible the use of loperamide should be avoided during the first trimester of pregnancy, however, it may be used during the second and third trimester of pregnancy.

Breast-feeding
Only very small amounts of loperamide hydrochloride may appear in human breast milk. Therefore, loperamide may be used during breast-feeding when dietary measures are insufficient and a drug-induced inhibition of intestinal motility is indicated.

Fertility
Only high doses of loperamide hydrochloride affected female fertility in non-clinical studies (see section 5.3).

4.7 Effects on ability to drive and use machines

Tiredness, dizziness, or drowsiness may occur in the setting of diarrheal syndromes treated with loperamide hydrochloride. Therefore, it is advisable to use caution when driving a car or operating machinery.

4.8 Undesirable effects

In this section frequencies of undesirable effects are defined as follows: 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).

Adolescents aged ≥ 12 years and adults
The safety of loperamide hydrochloride was evaluated in 3,076 adolescents aged ≥ 12 years and adults who participated in 31 controlled and uncontrolled clinical trials of loperamide hydrochloride used for the treatment of diarrhoea. Of these, 26 trials were in acute diarrhoea (n = 2,755) and 5 trials were in chronic diarrhoea (n = 321).

The most commonly reported adverse drug reactions (i.e., ≥ 1 % incidence) in clinical trials with loperamide hydrochloride in acute diarrhoea were constipation (2.7 %), flatulence (1.7 %), headache (1.2 %) and nausea (1.1 %). In clinical trials in chronic diarrhoea, the most commonly reported adverse drug reactions (i.e., ≥ 1 % incidence) were flatulence (2.8 %), constipation (2.2 %), nausea (1.2 %) and dizziness (1.2 %).

The table below displays adverse drug reactions from either clinical trial or post marketing experience.

Side effects classified according to system organ class	**Acute diarrhoea (n = 2,755)**	**Chronic diarrhoea (n = 312)**	**Acute and chronic diarrhoea following post marketing experience**
Immune system disorders			
Hypersensitivity reactions [a], anaphylactic reactions (including anaphylactic shock) [a], anaphylactoid reactions [a].			Rare
Nervous system disorders			
Headache.	Common	Uncommon	Common
Dizziness.	Uncommon	Common	Common
Somnolence [a].			Uncommon
Loss of consciousness [a], stupor [a], depressed level of consciousness [a], hypertonia [a], coordination abnormality [a].			Rare
Eye disorders			
Miosis [a].			Rare
Gastrointestinal disorders			
Constipation, nausea, flatulence.	Common	Common	Common
Abdominal pain and discomfort, dry mouth.	Uncommon	Uncommon	Uncommon
Abdominal pain upper, vomiting.	Uncommon		Uncommon
Dyspepsia.		Uncommon	Uncommon
Ileus [a] (including paralytic ileus), megacolon [a] (including toxic megacolon [b]), glossodynia [a].			Rare
Abdominal distension.	Rare		Rare
Acute pancreatitis			Not known

Skin and subcutaneous tissue disorders			
Rash.	Uncommon		Uncommon
Bullous eruption [a] (including Stevens-Johnson syndrome, Toxic epidermal necrolysis and erythema multiforme), angioedema [a], urticaria [a], pruritus [a].			Rare
Renal and urinary disorders			
Urinary retention [a].			Rare
General disorders and administration site conditions			
Fatigue [a].			Rare

[a] Inclusion of this term is based on post-marketing reports for loperamide hydrochloride. 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 hydrochloride (acute and chronic), including trials in children ≤ 12 years (n = 3,683).
[b] See section 4.4.

In the case of adverse reactions from clinical studies without frequency data, the adverse event was either not observed or was not considered as a side-effect for this indication.

Paediatric population
The safety of loperamide hydrochloride was evaluated in 607 patients aged 10 days to 13 years who participated in 13 controlled and uncontrolled clinical trials of loperamide hydrochloride used for the treatment of acute diarrhoea. In general, the ADR profile in this patient population was similar to that seen in clinical trials of loperamide hydrochloride in adolescents aged 12 years and over and adults.

Note
Some adverse events reported during clinical trials and after marketing of loperamide hydrochloride are often symptoms of the underlying diarrhoea (stomach pain, discomfort, nausea, vomiting, dry mouth, drowsiness, fatigue, dizziness, constipation and flatulence). These symptoms are often difficult to distinguish from the side effects of the drug.

Immediately after taking loperamide hydrochloride orodispersible tablets, some patients reported a temporary, burning or prickling sensation on the tongue.

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 overdose (including relative overdose due to hepatic dysfunction), CNS depression (stupor, coordination abnormality, somnolence, miosis, muscular hypertonia and respiratory depression), constipation, ileus and urinary retention may occur. Children may be more sensitive to CNS effects than adults.
In individuals who have ingested overdoses of loperamide hydrochloride (doses from 40 mg to 792 mg per day have been reported), cardiac events such as QT interval prolongation, 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.

Treatment
In cases of overdose, ECG monitoring for QT interval and QRS complex prolongation should be initiated.
If CNS symptoms occur after overdose, the opioid antagonist 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 (reoccurrence of) CNS depression.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antidiarrhoeals, intestinal antiinflammatory/antiinfective agents, antipropulsives
ATC code: A07DA03

Loperamide binds to the opiate receptor in the intestinal wall, thereby preventing the release of acetylcholine and prostaglandins, thus reducing propulsive peristalsis and increasing intestinal transit time. Loperamide increases the tone of the anal sphincter, which helps reduce faecal incontinence and urgency.

5.2 Pharmacokinetic properties

Absorption
Loperamide is primarily absorbed from the intestinal wall, 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 intestinal wall with a preference for binding to receptors of the longitudinal muscle layer. The plasma protein binding of loperamide is about 95 %, mainly to albumin. Nonclinical data have shown that loperamide is a P-glycoprotein substrate.

Biotransformation
In humans, loperamide is absorbed well from the intestine but is subject to almost complete extraction and metabolism by the liver where it is 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 plasma half-life of loperamide in humans is between 9 - 14 hours, with an average of approximately 11 hours. Excretion of the unchanged loperamide and the metabolites mainly occurs with the faeces.

Paediatric population
No pharmacokinetic studies were performed in the paediatric population. However, it is expected that pharmacokinetics and interactions with other drugs in this patient population are similar to those in adult patients.

5.3 Preclinical safety data

Acute and chronic studies on loperamide showed no specific toxicity. Results of in vivo and in vitro studies indicated that loperamide is not genotoxic. There was no carcinogenic potential.

Non-clinical in vitro and in vivo evaluation of loperamide hydrochloride indicate 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 flow, and arrhythmias.

In reproductive toxicity studies, very high doses of loperamide (40 mg/kg/day – corresponding to 27-fold the maximum daily dose in humans, based on body surface area) led to an impaired fertility in rats, as well as an adverse effect on foetal viability in association with maternal toxicity. Lower doses had no effect on maternal or foetal health and did not affect peri- or postnatal development.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol, aspartame, crospovidone, citric acid, silica colloidal anhydrous, spearmint (flavoring ingredients, modified food starch), talc, magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium/Aluminium blister.
Each pack contains 6, 10 and 12 orodispersible tablets or 6x1 orodispersible tablet in perforated unit dose blisters, 10x1 orodispersible tablet in perforated unit dose blisters and 12x1 orodispersible tablet in perforated unit dose blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No specific requirements.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd
Waterford Road
Clonmel, Co. Tipperary
E91 D768
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0126/305/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27th September 2019
Date of last renewal: 14th May 2024

10 DATE OF REVISION OF THE TEXT

August 2025