# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Loperamide 2 mg Capsules, hard

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 2mg loperamide hydrochloride.

Excipient(s) with known effect:

Each capsule contains 109.00 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Capsule, hard (Capsule)

Size '4' (about 14 mm in length) Hard gelatin capsule with Green cap imprinted with 'L' in black ink & grey body imprinted with '2mg' in black ink, containing white to off-white powder.

### 1.1 Therapeutic indications

For the symptomatic treatment of acute diarrhoea of any aetiology including acute exacerbations of chronic diarrhoea for periods of up to 5 days in adults and children over 9 years. For the symptomatic treatment of chronic diarrhoea in adults.

### 4.2 Posology and method of administration

*Posology*

*ACUTE DIARRHOEA*

*Adults and children over 12 years:*
Two capsules (4 mg) initially, followed by one capsule (2 mg) after each loose stool. The usual dose is 3-4 capsules (6 mg – 8 mg) a day. The total daily dose should not exceed 8 capsules (16 mg).

*Children 9 to 12 years*
One capsule (2 mg) four times daily until diarrhoea is controlled (up to 5 days). This dose should not be exceeded.

Further investigation into the cause of the diarrhoea should be considered if there is no improvement within two days of starting treatment with loperamide.

*CHRONIC DIARROHEA*

*Adults*
Patients may need widely differing amounts of loperamide. The starting dose should be between two and four capsules per day in divided doses, depending on severity. If required, this dose can be adjusted according to result up to a maximum of eight capsules daily.
Having established the patient's daily maintenance dose, loperamide may be administered on a twice daily regimen. Tolerance has not been observed and therefore subsequent dosage adjustment should be unnecessary.

*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, Loperamide 2 mg Capsules 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 use. The capsules should be taken with liquid.

## 4.3 Contraindications

Loperamide 2 mg Capsules are contraindicated:

- in patients with a known hypersensitivity to loperamide hydrochloride or to any of the excipients listed in section 6.1.
- in children less than 9 years of age.
- when inhibition of peristalsis is to be avoided due to the possible risk of significant sequelae including ileus, megacolon and toxic megacolon, in particular:
  - when ileus, constipation or abdominal distension develop,
  - 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.

Loperamide hydrochloride should not be used alone in acute dysentery, which is characterised by blood in stools and elevated body temperatures.

## 4.4 Special warnings and precautions for use

Caution is needed in patients with a history of drug abuse. Loperamide is an opioid and addiction is observed with opioids as a class.

Treatment of diarrhoea with Loperamide 2 mg Capsules 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 this medicine 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 Loperamide 2 mg Capsules should be discontinued and patients should be advised to consult their doctor.

Patients with AIDS treated with this medicine 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.

Although no pharmacokinetic data are available in patients with hepatic impairment, this medicine should be used with caution in such patients because of reduced first pass metabolism (eg in cases of severe hepatic disturbance), as it might result in a relative overdose leading to CNS toxicity.

Treatment with Loperamide must be discontinued promptly when constipation, abdominal distension or ileus develop.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine because it contains lactose.

Cardiac events including QT interval and QRS complex prolongation, torsade 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.

## 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 possesses any teratogenic or embryotoxic properties. As with other drugs, it is not advisable to administer loperamide 2 mg Capsules in pregnancy, especially in the first trimester.

Breast-feeding

Small amounts of loperamide may appear in human breast milk. Therefore, Loperamide 2 mg Capsules is not recommended during breast-feeding.

Women who are 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

Loss of consciousness, depressed level of consciousness, tiredness, dizziness, or drowsiness may occur when diarrhoea is treated with this medicine. 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); and very rare (<1/10,000).

*Table 1: Adverse Drug Reactions*

| **System Organ Class** | **Indication** | | |
|---|---|---|---|
| | **Common** | **Uncommon** | **Rare** |
| **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]) Abdominal distension |
| **Skin and Subcutaneous Tissue Disorders** | | Rash | Bullous eruption [a] (including Stevens-Johnson syndrome, Toxic epidermal necrolysis and Erythema multiforme) |

| | | | |
|---|---|---|---|
| | | | Angioedema [a]<br>Urticaria [a]<br>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 by searching for MHRA yellow card in the google play or Apple play 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, torsade 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 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 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

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 reproduction studies, very high doses (40 mg/kg/day – 20 times the maximum human use level (MHUL)), based on body surface area dose comparisons ($mg/m^2$), loperamide impaired fertility and fetal survival in association with maternal toxicity in rats. Lower doses (≥ 10mg/kg/day – 5 times MHUL) revealedno effects on maternal or fetal health and did not affect peri- and post-natal development.

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

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Lactose monohydrate,
Microcrystalline cellulose,
Maize starch,
Colloidal Anhydrous Silica,
Purified Talc,
Magnesium stearate.

Capsule cap:
Gelatin
Water
Sodium lauryl sulfate
Patent Blue V (E131)
Quinoline Yellow (E104)
Titanium Dioxide (E171)

Capsule body:
Gelatin
Water
Sodium lauryl sulfate
Brilliant Blue FCF (E133)
Iron Oxide Red (E172)
Titanium Dioxide (E171)

Printing ink:
Shellac (E904)

Propylene Glycol (E1520)
Black Iron Oxide (E172)
Potassium Hydroxide (E525)

### 6.2 Incompatibilities

Not applicable

### 6.3 Shelf life

36 months

### 6.4 Special precautions for storage

Store below 25°C. Store in the original package.

### 6.5 Nature and contents of container

Blister formed from PVC/PVdC and aluminium.
Packs of 2, 4, 6, 8, 12, 18 and 30 capsules.
Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

Not applicable.

## 7 MARKETING AUTHORISATION HOLDER

Flamingo Pharma (UK) Ltd
1st Floor, Kirkland House,
11-15 Peterborough Road,
Harrow, Middlesex,
HA1 2AX, United Kingdom

## 8 MARKETING AUTHORISATION NUMBER(S)

PL 43461/0011

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

27/01/2017

## 10 DATE OF REVISION OF THE TEXT

08/02/2021