SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Imolopera 2 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 mg loperamide hydrochloride.

Excipient with known effect:
Lactose (101 mg).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet (white, round, one side marked C and the other side marked 11).
Diameter: 6.5 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic treatment of acute non-specific diarrhoea and chronic diarrhoeal conditions, including excessive bowel passage, with or without faecal incontinence and in conjunction with ileostomies, colostomies and dumping.

4.2 Posology and method of administration

Posology

Acute diarrhoea: 4 mg (2 tablets) initially, followed by 2 mg (1 tablet) after each stool with diarrhoea. However, wait 2-3 hours between the first and second dose. The total daily dose should not exceed 16 mg (8 tablets).

Chronic diarrhoeal conditions: the treatment is initiated with 4 mg (2 tablets). The dosage is then adjusted individually within the range of 2-16 mg (1-8 tablets) daily. However, the lowest possible maintenance dose should be aimed for. Often 1-2 doses daily are sufficient. The daily dose should not exceed 16 mg (8 tablets).

Children under 12 years of age
Limited data are available regarding the treatment of children under 12 years of age. See section 4.8.

Elderly
No dose adjustment is required for elderly patients.

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 [Invented name] should be used with caution in these patients due to reduced first pass metabolism (see section 4.4).

Method of administration
For oral use.
The tablets should be taken with liquid.

4.3 Contraindications

- [Invented name] is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- [Invented name] must not be given to children less than 12 years of age.
- [Invented name] must not be used as first-line therapy in patients with:
  - acute dysentery, which is characterized by blood in stool and high fever.
  - acute ulcerative colitis or pseudomembranous colitis as a result of treatment with antibiotics.
  - bacterial enterocolitis caused by invasive organisms including Salmonella, Shigella and Campylobacter.

[Invented name] 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. [Invented name] must be discontinued promptly if constipation, abdominal distension or ileus develop.

4.4 Special warnings and precautions for use

In chronic inflammatory bowel diseases since loperamide can mask the symptoms of acute deterioration. Treatment with [Invented name] is only symptomatic, therefore causal therapy should be given first .

Dehydration and electrolyte disturbances may occur in patients with diarrhoea, especially in children. It is important to pay attention to appropriate fluid and electrolyte substitution. Treatment with [Invented name] should be discontinued if there are signs of constipation or other signs of insufficient peristalsis. If clinical effect is not observed within 2 days of acute diarrhoea, [Invented name] should be discontinued and the patient should be advised to consult a doctor.

Patients with AIDS treated with [Invented name] for diarrhoea, should have the treatment discontinued at the first sign of abdominal distension. There have been isolated reports of obstipation with an increased risk of toxic megacolon in AIDS patients with infectious colitis caused by both viral and bacterial pathogens treated with loperamide hydrochloride.

Although no pharmacokinetic data are available in patients with hepatic impairment, [Invented name] should be used with caution in such patients due to reduced first pass metabolism. This medicine must be used with caution in patients with hepatic impairment as it may result in a relative overdose leading to CNS toxicity.

Overdose can unmask existing Brugada syndrome.

Cardiac events including QT prolongation and torsades de pointes have been reported in association with overdose. Some cases had a fatal outcome (see section 4.9). Patients should not exceed the recommended dose and/or the recommended duration of treatment.

Combination with high-dose loperamide and drugs that inhibit P-glycoprotein (quinidine, ritonavir, cyclosporine, verapamil and certain macrolide antibiotics, e.g. erythromycin and clarithromycin) should be used with caution (see section 4.5).

There are limited data available regarding the treatment of children under 12 years of age. See section 4.8.

[Invented name] tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Cholestyramine can possibly reduce the absorption of loperamide. The medications should not be taken at the same time, but at intervals of a couple of hours.
Loperamide is a substrate for the transport protein P-glycoprotein, which i.a. is found in the blood-brain barrier. Concomitant administration of loperamide (16 mg as a single dose) with quinidine or ritonavir, both p-glycoprotein inhibitors, resulted in a 2- to 3-fold increase in loperamide plasma levels. Theoretically, increased distribution to the CNS can also occur. The clinical relevance of this pharmacokinetic interaction, when loperamide is given in recommended doses, is incompletely known, but the risk of centrally decreased sensitivity to carbon dioxide and thus an effect on respiration cannot be excluded (see section 4.4).

Combination with high doses of loperamide and drugs that inhibit P-glycoprotein, e.g. quinidine, ritonavir, cyclosporine, verapamil and certain macrolide antibiotics, e.g. erythromycin and clarithromycin should be used with caution. Dose adjustment should be considered (see section 4.4).

Concomitant administration of loperamide (4 mg as a 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 the plasma concentration of loperamide 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 Digit Symbol Substitution test).

Concomitant administration of loperamide (16 mg as a 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 measured by pupillometry.

Concomitant treatment with oral desmopressin resulted in a 3-fold increase in 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 the gastrointestinal transit may decrease the effect of loperamide.

4.6 Fertility, pregnancy and lactation

Pregnancy
Clinical experience in pregnant women is limited. Studies in rats have shown increased fetal mortality at high doses. Although there are no indications that [Invented name] has teratogenic or embryotoxic properties, the expected therapeutic benefits should be weighed against the potential risks before [Invented name] is given during pregnancy, especially during the first trimester.

Breast-feeding
Small amounts of loperamide may appear in breast milk. Therefore [Invented name] is not recommended during breast-feeding.

Women who are pregnant or breastfeeding should be advised to consult a doctor for appropriate treatment.

4.7 Effects on ability to drive and use machines

Fatigue, dizziness and drowsiness may occur during treatment with [Invented name]. This should be taken into account when increased attention is required, e.g. when driving or using machinery.

4.8 Undesirable effects

Adults and children ≥12 years of age
The safety of loperamide hydrochloride was evaluated in 3076 adults and children aged ≥12 years who participated in 31 controlled and uncontrolled clinical trials of loperamide hydrochloride used for the

treatment of diarrhoea. Of these, 26 trials concerned acute diarrhoea (N=2755) and 5 trials concerned chronic diarrhoea (N=321).

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

The table shows adverse reactions that have been reported with the use of loperamide hydrochloride from either clinical trials (acute or chronic diarrhoea or both) or from post-marketing experience.

The frequency categories are based on 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).

System Organ Class	**Indication**		
	Acute diarrhoea (N=2755)	**Chronic diarrhoea (N=321)**	**Acute + chronic diarrhoea and post-marketing experience**
Immune system disorders			
Hypersensitivity reactions[a], anaphylactic reaction (including anaphylactic shock)[a], anaphylactoid reaction[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, abdominal discomfort, dry mouth	Uncommon	Uncommon	Uncommon
Upper abdominal pain, vomiting	Uncommon		Uncommon
Dyspepsia		Uncommon	Uncommon
Ileus[a] (including paralytic ileus), megacolon[a] (including toxic megacolon[b]), glossodynia[a,c]			Rare
Abdominal distension	Rare		Rare
Acute pancreatitis	Not known (cannot be estimated from the available data)	Not known (cannot be estimated from the available data)	Not known (cannot be estimated from the available data)
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 adverse reactions did not differentiate between chronic and acute indications or adults and children, the frequency is estimated from all clinical trials with loperamide hydrochloride combined, including trials in children ≤12 years (N=3683).
b: See section 4.4 Warnings and precautions.
c: Reported for orodispersible tablet only.
Adverse reactions in clinical trials listed without frequency were not observed or evaluated as adverse reactions 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 adverse reaction profile for this patient population was similar to the one seen in clinical trials of loperamide hydrochloride in adults and children ≥ 12 years.

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 national reporting system listed in Appendix V.

4.9 Overdose

Toxicity: 1-2 mg daily given to 1-6 month old children caused severe - very severe intoxication.
10 mg given to 4 month old children caused very severe intoxication. 3 mg distributed over 16 hours to a 4 years old child caused moderate intoxication. While 1 mg to a 1½ year old child as well as a maximum 12 mg to a 2 year old child (who was gastric emptied) gave mild intoxication. 26 mg to an adult produced no symptoms after gastric emptying.

Symptom: Symptoms are often delayed and in children they may appear after repeated therapeutic dosing. In overdose (including relative overdosage due to hepatic impairment), central nervous system depression (stupor, coordination difficulties, somnolence, miosis, muscular hypertonia, respiratory depression), apathy, dizziness, confusion, hallucinations, depressed level of consciousness, coma, apnea, increased or decreased muscle tone, opisthotonus, bradycardia, VES, hyperglycaemia, nausea, vomiting, constipation, urinary retention and ileus may occur. Children may be more sensitive to central nervous system effects than adults.

In individuals who have ingested overdoses of loperamide hydrochloride, 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: As the strategies for managing overdose are constantly evolving, it is advisable to contact the Poison Information Center to see the latest recommendations for managing an overdose.

If justified, coal. In CNS and respiratory depression, naloxone can be given as an antidote. Since loperamide is longer acting than naloxone, repeated treatment with naloxone may be necessary. Therefore, the patient should be closely monitored for at least 48 hours to detect possible CNS depression. Symptomatic treatment is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antipropulsives, ATC code: A07DA03

Loperamide binds to the opiate receptor in the intestinal wall, thereby inhibiting the release of acetylcholine and prostaglandins. Thereby the propulsive peristalsis is reduced and the transit time in the intestine is extended, which enhances the reabsorption of water and electrolytes. Loperamide increases anal sphincter tone , thereby reducing faecal congestion and faecal incontinence. Loperamide does not affect the normal flora of the intestine.

In a double-blind randomized clinical trial conducted in 56 patients with acute diarrhoea receiving loperamide, antidiarrhoeal effect was observed within one hour after 4 mg as a single dose.

5.2 Pharmacokinetic properties

Absorption
The majority of ingested loperamide is absorbed from the intestine, but as a result of significant first pass metabolism, systemic bioavailability is only about 0.3%.

Distribution
Studies on distribution in rats show high affinity for the intestinal wall with a preference for binding to receptors in the longitudinal muscle layer. The plasma protein binding of loperamide is 95%, mainly to albumin. Preclinical data have shown that loperamide is a substrate to p-glycoprotein.

Metabolism
Loperamide is almost completely eliminated by the liver, where it is predominantly metabolized, conjugated and excreted via the bile. Loperamide is mainly metabolized by oxidative N-demethylation via CYP3A4 and CYP2C8. Due to this very high first pass effect, plasma concentrations of unchanged drug are extremely low.

Elimination
The half-life in humans is about 11 hours (interval 9-14 hours). Metabolites and unchanged loperamide are mainly excreted via faeces.

5.3 Preclinical safety data

Acute and chronic studies on loperamide showed no specific toxicity. Results from studies performed *in vivo* and *in vitro* indicate that loperamide is not genotoxic. High doses (40 mg/kg/day - 20 times higher than human dose based on body surface area comparison) of loperamide given in reproduction studies led to reduced fertility and fetal survival in rats at maternally toxic doses. Lower doses (≤10 mg/kg - 5 times higher than human dose based on body surface comparison) had no effect on maternal or fetal health and did not affect peri- and postnatal 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, anhydrous
Maize starch

Polysorbate 80
Talc
Silica, colloidal anhydrous
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

Blister pack (PVDC/PVC/Aluminium).

Blister pack sizes: 16, 20, 40, 100 and 104 tablets.
Plastic container (HDPE): 250 tablets (only for dose dispensing).
Plastic container (HDPE): 250 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

2023-03-14