SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Loperamide Medical Valley 2 mg tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 mg loperamide hydrochloride.

Excipients with known effect:
Lactose 101 mg per tablet.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets (white to off-white, 6.5 mm, round, biconvex, uncoated tablets debossed with “C” on one side and “11” on other side).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic treatment of acute nonspecific diarrhoea and chronic diarrhoea, 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: Treatment starts with 4 mg (2 tablets). Then 2 mg (1 tablet) after each stool with diarrhoea. However, wait 2-3 hours between the first and second dose. The daily dose should not exceed 16 mg (8 tablets).

Chronic diarrhoea conditions: Treatment is initiated with 4 mg (2 tablets). The dosage is then adjusted individually within the range of 2-16 mg (1-8 tablets)/day, with the lowest possible maintenance dose being sought. Often 1-2 doses daily are sufficient. The daily dose should not exceed 16 mg (8 tablets).

Paediatric population
The safety and efficacy of [Invented name] in children under 12 years have not yet been established. Currently available data are described in section 4.8 but no recommendation on a posology can be made.

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 for 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
The tablets should be taken with liquid

4.3 Contraindications

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- age under 12 years.
- not to be used as the primary therapy in patients with:
  - acute dysentery characterised by blood in stools 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.

- not to be used to prevent peristalsis inhibition due to the risk of significant sequelae, including ileus, megacolon and toxic megacolon
- [Invented name]must be discontinued immediately if constipation, abdominal distention or ileus develops.

4.4 Special warnings and precautions for use

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

Dehydration and electrolyte disturbances can 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 signs of constipation or other signs of insufficient peristalsis are observed. If clinical effect is not noted within two days of acute diarrhoea, [Invented name] should be discontinued and the patient should be advised to consult a physician.

In patients with AIDS treated with [Invented name]for diarrhoea, treatment should be discontinued at the first sign of abdominal distention. Isolated cases of constipation with an increased risk of toxic megacolon have been reported in AIDS patients with infectious colitis caused by both viruses and bacteria treated with loperamide hydrochloride.

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

Cardiac side effects, including extended QT interval and QRS complexes and torsades de pointes, have been reported in association with overdose. Some cases have had a fatal outcome (see section 4.9). Overdose may reveal existing Brugada syndrome. Patients should not exceed the recommended dose and/or the recommended treatment time.

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

Limited data are 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 Interactions with other medicinal products and other forms of interaction

Cholestyramine possibly reduces the absorption of loperamide. The medications should not be used at the same time but at intervals of a few hours.
Loperamide is a substrate for the transport protein P-glycoprotein, which inter alia is found in the blood-brain barrier. Co-administration of loperamide (single-dose 16 mg) with quinidine or ritonavir, both of which are P-glycoprotein inhibitors, resulted in a 2- to 3-fold increase in loperamide plasma levels. Theoretically, increased distribution to the CNS can also be obtained. The clinical relevance of this pharmacokinetic interaction, when loperamide is given at the recommended doses, is incompletely

known, but the risk of centrally reduced sensitivity to carbon dioxide and thus the effects on respiration cannot be ruled out (see section 4.4).

Combination of high dose of loperamide and drugs that inhibit P-glycoprotein eg. 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).

Co-administration of loperamide (single-dose 4 mg) with 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 the maximum plasma levels of loperamide and a 13-fold increase in total plasma exposure. These increases were not associated with CNS effects measured by psychomotor tests (i.e., subjective drowsiness and Digit Symbol Substitution test).

Co-administration of loperamide (single-dose 16 mg) with 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 in desmopressin plasma concentrations, probably due to slower gastrointestinal motility.

It is expected that drugs with the same pharmacological properties can potentiate the effect of loperamide and that drugs that accelerate the gastrointestinal passage may reduce the effect of loperamide.

4.6 Pregnancy and lactation

Pregnancy
Clinical experience in pregnant women is limited. Trials 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.

Breastfeeding
Small amounts of loperamide can occur in breast milk. Therefore, [Invented name] is not recommended during breastfeeding.

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 machines.

4.8 Undesirable effects

Adults and children ≥ 12 years

The safety of loperamide hydrochloride was evaluated in 3076 adults and children ≥ 12 years of age who participated in 31 controlled and uncontrolled clinical trials of loperamide hydrochloride used to treat diarrhoea. Of these, 26 were for acute diarrhoea (N = 2755) and 5 for chronic diarrhoea (N = 321).

The most commonly reported (ie ≥ 1% incidence) side effects 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 (i.e., ≥ 1% incidence) adverse reactions 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 either from clinical trials (in acute or chronic diarrhoea or both) or from 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) and 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 reaction[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
Abdominal pain upper, Vomiting	Uncommon		Uncommon
Dyspepsia		Uncommon	Uncommon
Ileus[a] (including paralytic ileus), megacolon (including toxic megacolon[b]), glossodynia[a,c]			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 lopermide hydrochloride. Since the process for determining post-marketing adverse events does not differentiate between chronic and acute indications or adults and children, the frequency is an estimate from all clinical trials with loperamide hydrochloride, including trials for children ≤ 12 years (N = 3683).
[b]: see section 4.4 Warnings and cautions.
[c]. Reported for orodispersible tablet only.
Adverse reactions in clinical trials stated without frequency were not observed or evaluated as adverse events for this indication.

Pediatric 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 to treat acute diarrhoea. In general, the adverse reaction profile for this patient population was similar to that 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/day to 1-6 month old children gave severe - very severe intoxication. 10 mg to 4 month old children gave very severe intoxication. 3 mg distributed over 16 hours to 4-year-old gave moderate, while 1 mg to 1 1/2-year-old as well as max 12 mg to 2-year-old (who were gastric emptied) gave mild intoxication. 26 mg for adults after ventricular emptying did not produce any symptoms.

Symptoms: Symptoms are often delayed and may in children occur after repeated therapeutic dosing. In overdose (including relative overdose caused by hepatic impairment), CNS depression (drowsiness, coordination difficulties, somnolence, miosis, muscle hypertension and respiratory depression), apathy, dizziness, confusion, hallucinations, reduced consciousness, coma, apnea, increased or decreased muscular tone, opisthotonos, bradycardia,VES, hyperglycemia, nausea, vomiting, constipation, urinary retention and ileus occur. Children may be more sensitive to CNS effects than adults.

In individuals who have overdosed with loperamide, cardiac side effects such as prolonged QT interval and QRS complex, torsades de pointes, other severe ventricular arrhythmias, cardiac arrest and syncope have been observed (see section 4.4). Cases with fatal outcome have also been reported. Overdose may reveal 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: 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 acetykoline and prostaglandins. Thereby, the propulsive peristalsis decreases and the passage time in the intestine is prolonged, which increases the uptake of water and electrolytes. Loperamide increases anal sphincter tone, thereby reducing faecal congestion and faecal incontinence.
Loperamide does not affect the normal flora in the intestine.

In a double-blind, randomized clinical trial performed on 56 patients with acute diarrhoea receiving loperamide, diarrhoea-antagonizing effects were observed within one hour after 4 mg as a single dose.

5.2 Pharmacokinetic Properties

Absorption

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

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

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

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

5.3 Pre-clinical Safety Data

Acute and chronic loperamide studies showed no specific toxicity. Results from *in vivo* and *in vitro* studies 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 maternal toxic doses. Lower doses (≤10 mg/kg - 5 times higher than human dose based on body surface comparison) showed no effect on maternal or fetal health and did not affect peri- and postnatal development.

In vitro and *in vivo* toxicological evaluation of loperamide shows no significant electrophysiological cardiac effects within the treatment-relevant concentration range or at relevant multiples of this range (up to 47 times). However, at extremely high concentrations associated with overdose (see section 4.4), loperamide has electrophysiological cardiac effects consisting of inhibition of potassium (hERG) and sodium currents as well as arrhythmias.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose
Maize starch
Polysorbate 80 (E433)
Talc (E553b)
Colloidal anhydrous silica
Magnesium stearate (E572)

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 (PVC/PVDC/aluminium): 20 and 60 tablets.
HDPE bottle (PP cap with liner): 45, 105 and 270 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special precautions.

7. MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>
{Name and address}

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION / RENEWED AUTHORISATION

<Date of first authorisation: {DD month YYYY}>

10. DATE OF REVISION OF THE TEXT

2025-03-13