SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Lopacut 2 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 mg of loperamide hydrochloride.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

White, round and convex tablet with logo “6”. Diameter is 8 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the symptomatic short-term treatment of acute diarrhoea.
Lopacut is indicated in adults and adolescents over 12 years.

4.2 Posology and method of administration

Posology

Adults and adolescents over 12 years of age
Two tablets initially, followed by 1 tablet after every loose stool, not earlier than 2-3 hours after the initial dose. The maximum daily dose should not exceed 6 tablets (12 mg) for adults and 4 tablets (8 mg) for adolescents. If there is no improvement within two days, the treatment with Lopacut should discontinue.

The elderly
No dosage adjustment is required for the elderly.

Renal Impairment
No dosage adjustment is required for patients with renal impairment.

Hepatic Impairment
Loperamide should be used with caution in patients with hepatic impairment (see section 4.4).

Method of administration

Oral use.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

- Age under 12 years.
- Loperamide should not be used as the primary therapy in patients with:
  - Acute dysentery, characterised by blood in stools and a high fever.
  - Acute ulcerative colitis or pseudomembranous colitis associated with the use of broad-spectrum antibiotic treatment.
  - Bacterial enterocolitis caused by invasive organisms including Salmonella, Shigella, and Campylobacter.

- When inhibition of peristalsis should be avoided, because of risk of significant sequels including ileus, megacolon or toxic megacolon.
- Chronic diarrhoea
- Loperamide must be discontinued promptly when constipation, abdominal distension or ileus develop.

4.4 Special warnings and precautions for use

In chronic inflammatory bowel diseases loperamide may mask the symptoms of acute deterioration.

The priority in acute diarrhoea is the prevention or reversal of fluid and electrolyte depletion. This is particularly important in children and in frail and elderly patients with acute diarrhoea. In such cases administration of appropriate fluid and electrolyte replacement therapy is the most important measure.

The treatment of diarrhea with loperamide is symptomatic only. If specific underlying causes of diarrhoea can be identified, specific treatment should be given when appropriate.

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

Since persistent diarrhoea can be an indicator of potentially more serious conditions, loperamide should not be used for prolonged periods until the underlying cause of the diarrhoea has been investigated.

Although no pharmacokinetic data are available in patients with hepatic impairment, loperamide must be used with caution in such patients because of 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.

Patients with AIDS treated with loperamide 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.

Combination of high dose loperamide and medicinal products that inhibit P-glycoprotein (e.g. quinidine, ritonavir, cyclosporin, verapamil, and some macrolide antibiotics, e.g. erythromycin and clarithromycin) should be performed with caution (see section 4.5).

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

<u>Cholestyramine</u>

Concomitant administration of cholestyramine may decrease absorption of loperamide.

P-glycoprotein inhibitors
Non-clinical studies have shown that loperamide is a substrate for P-glycoprotein, which for example can be found in the blood-brain barrier. Concomitant use 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. Theoretically, an increased distribution to the CNS could occur as well. The clinical relevance of this pharmacokinetic interaction with P-glycoprotein inhibitors, when loperamide is given at recommended dosages (2 mg, up to 12 mg maximum daily dose), is unknown, but a risk for a centrally decreased sensitivity for carbon dioxide and thereby an effect on respiration cannot be excluded. Combination of high dose loperamide and medicinal products that inhibit P-glycoprotein, e.g. quinidine, ritonavir, cyclosporin, verapamil, and some macrolide antibiotics, e.g. erythromycin and clarithromycin, should be performed with caution. Dose adjustment may be considered.

Itraconazole
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).

Ketoconazole
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.

Desmopressin
Concomitant treatment with oral desmopressin resulted in a 3-fold increase of desmopressin plasma concentrations, presumably due to slower gastrointestinal motility.

Anticholinergics
Anticholinergics slow stomach and bowels emptying and the effect of loperamide may be stronger.

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
There is limited amount of clinical data in pregnant women. Studies in rats have shown increased foetal mortality at high doses. Therefore, until further experience is gained, loperamide should be given only after careful consideration during pregnancy. Although there are no indications that loperamide possesses teratogenic or embryotoxic properties, the anticipated therapeutic benefits should be weighed against potential hazards before loperamide is given during pregnancy, especially during the first trimester.

Breast-feeding
Small amounts of loperamide may appear in human breast milk. Therefore, loperamide HCl is not recommended during breast-feeding.

4.7 Effects on ability to drive and use machines

Tiredness, dizziness and drowsiness may occur in the setting of diarrheal syndromes treated with Lopacut. Therefore, it is advisable to use caution when driving car or operating machinery (see section 4.8).

4.8 Undesirable effects

Adults and children aged ≥12 years

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

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%). In clinical trials in chronic diarrhoea, the most commonly reported (i.e., ≥1% incidence) ADRs were: flatulence (2.8%), constipation (2.2%), nausea (1.2%) and dizziness (1.2%).

The frequency classification of adverse effects is following:

- 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 (can not be estimated from the available data)

The following undesirable effects have been reported in either clinical trials or post-marketing experience with loperamide:

Immune system disorders:	
rare:	allergic reaction/hypersensitivity reaction[a] and in some cases severe hypersensitivity reactions including anaphylactic reaction (including anaphylactic shock) [a], anaphylactoid reaction[a]
Psychiatric disorders:	
not known:	drowsiness
Nervous system disorders:	
common:	dizziness, headache
uncommon:	somnolence[a]
rare:	loss of consciousness[a], stupor[a], decreased level of consciousness[a], hypertonia[a], coordination abnormality[a]
Eye disorders:	
rare:	miosis
Gastrointestinal disorders:	
common:	constipation, nausea, flatulence, abdominal cramping and colic
uncommon:	abdominal pain, abdominal discomfort, dryness of mouth, abdominal pain upper, vomiting, dyspepsia
rare:	ileus[a] (including paralytic ileus), abdominal distension, megacolon[a] (including toxic megacolon[b])
not known:	acute pancreatitis

Skin and subcutaneous tissue disorders:

uncommon:	rash
rare:	urticaria[a], pruritus[a], angioedema[a], bullous eruptions[a] including Stevens-Johnson Syndrome, erythema multiforme, and toxic epidermal necrolysis

Renal and urinary disorders:

rare:	urinary retention[a]

General disorders and administration site conditions:

rare:	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 combined, including trials in children ≤12 years (N=3683).
b: See section 4.4 Special warnings and precautions for use.

Paediatric population
The safety of loperamide HCl was evaluated in 607 patients aged 10 days to 13 years who participated in 13 controlled and uncontrolled clinical trials of loperamide HCl 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 HCl in adults and children aged 12 years and over.

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 for children 1-6 months of age resulted serious-very serious intoxication. 10 mg for children aged 4 months resulted in very severe intoxication. 3 mg during 16 hours to 4 year old gave moderate intoxication, while 1 mg to 1 ½ year old and maximum of 12 mg to 2 year old (who was treated with gastric lavage) gave mild intoxication. 26 mg to an adult did not give any symptoms after gastric lavage.

Symptoms:
Symptoms are often delayed and can occur in children after repeated therapeutic doses. In case of overdose (including relative overdose due to hepatic dysfunction), CNS depression (stupor, coordination abnormality, somnolence, miosis, muscular hypertonia, and respiratory depression), urinary retention and ileus may occur. Lethargy, dizziness, confusion, hallucinations, decreased consciousness, coma. Apnea. Increased or decreased muscle tone, opisthotonus. Bradycardia, ventricular extrasystoles. Hyperglycemia. Nausea, vomiting, constipation, and in rare cases, paralytic ileus. Children may be more sensitive to CNS effects than adults.

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:
If justified gastric lavage, activated charcoal. Monitoring should be extended to 24 hours if a large dose has been taken. If 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. In case of CNS and respiratory depression, naloxone 0.4 mg IV (For children 0.01 mg / kg IV) is given repeatedly until the effect is obtained and then again when necessary. Possibly controlled breathing. In dystonic reactions, muscle cramps are given diazepam. Symptomatic therapy.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antipropulsives
ATC Code – A07DA03

Loperamide hydrochloride is a synthetic opioid which inhibits gut motility by binding to opiate receptors in the gut wall and may also reduce gastrointestinal secretions, resulting in improvement in diarrhoea symptoms. Loperamide also increases the tone of the anal sphincter. Onset of antidiarrhoeal effect occurred as soon as one hour after intake of a 4 mg dose of loperamide.

5.2 Pharmacokinetic properties

Absorption
Loperamide is well absorbed from the gut.

Biotransformation
Loperamid is almost completely extracted and metabolised by the liver where it is conjugated and excreted via the bile in faeces. Due to its high affinity for the gut wall and its high first pass metabolism, very little loperamide reaches the systemic circulation.

Elimination
The elimination half life is reported to be about 11 hours (9-14 hours).

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 with loperamide and its pro-drugs *e.g.* loperamidoxide indicated that loperamide is not genotoxic. In reproductive toxicity studies in rats, very high doses (40 mg/kg/day - 240 times the maximum human dose) of loperamide, associated with maternal toxicity, impaired fertility and foetal survival. Lower doses had no effects on maternal or foetal 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

Tablet core:
Cellulose, microcrystalline

Starch, pregelatinized
Croscarmellose sodium
Silica, colloidal anhydrous
Magnesium stearate

Tablet coating:
Polydextrose
Hypromellose
Titanium dioxide (E 171)
Macrogol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

8 and 10 film-coated tablets in blister (PVC/Al).

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

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Varastokatu 8
FI-13500 Hämeenlinna
FINLAND
Tel: +358 (3) 615600
Fax: +358 (3) 6183130

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

2022-06-01