SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Vacontil 2 mg capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains loperamide hydrochloride 2 mg.

Excipient with known effect: lactose monohydrate.
For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule, hard.
Dark green - Grey gelatine capsules size ‘4’.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Symptomatic treatment of acute diarrhoea of any aetiology for periods of up to 2 days in adults and children aged 12 years and over.

4.2. Posology and method of administration

Posology

Adults and children 12 years and over:
Two capsules initially, followed by one capsule after each loose stool. The usual dose is 3-4 capsules per day. The total daily dose should not exceed 6 capsules.

Paediatric population
There is limited data available regarding use in children below 12 years of age (see section 4.8).
Loperamide is contraindicated in children less than 12 years of age.
Further investigation into the cause of the diarrhoea should be considered if there is no improvement within two days of starting treatment with loperamid.

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 should be used with caution in such patients because of reduced first pass metabolism (see section 4.4).

Method of administration
Oral use
The capsules should be taken with liquid.

4.3. Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- In children aged 12 and under.
- 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 bread-spectrum antibiotics.
- Loperamid should not be used alone in patients with acute dysentery, which is characterised by blood in stools and high fever.

4.4. Special warnings and precautions for use

Treatment of diarrhoea with loperamide 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 particular in young children and in frail and the elderly with acute diarrhoea. Use of loperamide 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.
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, as it may result in a relative overdose leading to CNS toxicity.
Loperamid must be discontinued promptly when constipation, abdominal distension or ileus develop.
In acute diarrhoea, if clinical improvement is not observed within 48 hours, the administration of loperamide 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 obstipation with an increased risk for toxic megacolon in AIDS patients with infectious colitis from both viral and bacterial pathogens treated with loperamide hydrochloride.
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.

Vacontil contains lactose monohydrate. 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

Non-clinical data have shown that loperamide is a P-glycoprotein substrate. Concomitant administration of loperamide (16 mg single dose) with quinidine or ritonavir, that are P-glycoprotein inhibitors, resulted in elevated 2-3 fold plasma concentrations of loperamide. The clinical relevance of this pharmacokinetic interaction with P-glycoprotein inhibitors when loperamide is given at recommended dosages (2mg, up to 16mg maximum daily dose) is not known.
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 have not demonstrated any teratogenic or embryotoxic effects. As with other drugs, it is not advisable to administer this medicine in pregnancy, especially during the first trimester.

Breast-feeding
Small quantities of loperamide are excreted in breast milk, therefore loperamide is not recommended during breast feeding.
Women who are pregnant or breast feeding infants should therefore be advised to consult their doctor for appropriate treatment.

4.7. Effects on ability to drive and use machines

Tiredness, drowsiness and dizziness 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.

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); not known (cannot be estimated from the available data).

Table 1: Adverse Drug Reactions

System Organ Class	*ADRs*			
	Common	*Uncommon*	*Rare*	*Not Known*
Immune System Disorders			Hypersensitivity reaction Anaphylactic reaction (including Anaphylactic shock) Anaphylactoid reaction	
Nervous System Disorders	Headache	Dizziness Somnolence	Loss of consciousness Stupor Depressed level of consciousness Hypertonia Coordination abnormality	
Eye Disorders			Miosis	
Gastrointestinal Disorders	Constipation Nausea Flatulence	Abdominal pain Abdominal discomfort Dry mouth Abdominal pain upper Vomiting Dyspepsia	Ileus (including paralytic ileus) Megacolon(including toxic megacolon*) Abdominal distension	Acute pancreatitis
Skin and Subcutaneous Tissue Disorders		Rash	Bullous eruption(including Stevens-Johnson syndrome, Toxic epidermal necrolysis and Erythema multiforme)	

System Organ Class	*ADRs*			
	Common	*Uncommon*	*Rare*	*Not Known*
			Angioedema Urticaria Pruritus	
Renal and Urinary Disorders			Urinary retention	
General Disorders and Administration Site Conditions			Fatigue	

*See section 4.4.

A number of the adverse events reported during the clinical investigations and post-marketing experience with loperamide are frequent symptoms of the underlying diarrhoeal syndrome (for example abdominal pain/discomfort, nausea, vomiting, dry mouth, tiredness, drowsiness, dizziness, constipation and flatulence). These symptoms are often difficult to distinguish from undesirable drug effects.

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.

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, ileus may occur. Children and patients with hepatic dysfunction may be more sensitive to CNS effects.

In individuals who have ingested overdoses of loperamide HCl, cardiac events such as QT interval and QRS complex prolongation and/or serious ventricular arrhythmias including torsades de pointes, 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 may 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.

Upon cessation, cases of drug withdrawal syndrome, have been observed in individuals abusing, misusing or intentionally overdosing with excessively large doses of loperamide.

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.

Paediatric Population: No pharmacokinetic studies were performed in the paediatric population. It is expected that pharmacokinetic behaviour of loperamide and drug-drug interactions with loperamide will be similar to those in adults.

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 comparison (mg/m2), loperamide impaired fertility and foetal survival in association with maternal toxicity in rats. Lower No Observed Adverse Effect Levels (NOAEL) doses (≥ 10mg/kg/day – 5 times MHUL) revealed 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

Capsule core
Lactose monohydrate
Pregelatinized maize starch
Talc
Magnesium stearate

Capsule shell
Gelatin
Sunset yellow (E110)
Brilliant blue (E133)
Erythrosine (E127)
Titanium dioxide (E171)

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

5 years.

6.4. Special precautions for storage

Store below 25ºC, in the original package, in order to protect from light and moisture.

6.5. Nature and contents of container

Blister boxes with 10 or 20 capsules.
Blister boxes with 30 or 1000 capsules.
Not all pack sizes may be marketed.

6.6. Special precautions for disposal

Not applicable

7. MARKETING AUTHORISATION HOLDER

Medochemie Ltd, 1-10 Constantinoupoleos Street 3011, Cyprus

8. MARKETING AUTHORISATION NUMBER

08105/08038/VAR/2022

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorisation: 26/03/2013
Date of latest renewal: 10/08/2021

10. DATE OF REVISION OF THE TEXT

28/06/2023