SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Norimode 2mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMSITION

Each tablet contains 2mg of Loperamide Hydrochloride.

Excipients with known effect:

Each Norimode 2mg tablet contains 110.356 mg Lactose

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

White, round, biconvex tablet of diameter 6.35mm, marked “T3” on one side, scored on reverse

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

The symptomatic treatment of acute diarrhoea of any aetiology including acute exacerbations of chronic diarrhoea for periods of up to five days, in adults and children over nine years.

The symptomatic treatment of chronic diarrhoea in adults.

4.2 Posology and method of administration

Posology:

Acute Diarrhoea

Adults and Children (9-17) years:
The initial dose is two tablets (4mg) for adults and one tablet (2mg) for children, followed by one tablet (2mg) after every subsequent loose stool for up to five days.

The maximum daily dose should not exceed six tablets (12mg).

Chronic Diarrhoea

Adults only
The initial dose is two tablets (4mg) daily. This initial dose should be adjusted until one to two solid stools per day are obtained, which is usually achieved with a maintenance dose of one to six tablets (2mg – 12mg) daily.

The maximum daily dose should not exceed six tablets (12mg).

Paediatric Population
Loperamide is contraindicated in children less than 9 years of age.

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 HCl should be used with caution in such patients because of reduced first pass metabolism. (See section 4.4 Special warnings and precautions for use).

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

4.3 Contraindications

The medicine is contraindicated:

- Patients with a known hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- In children under 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 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

In patients with diarrhoea, especially young children, fluid and electrolyte depletion may occur. Use of loperamide does not preclude the administration of appropriate fluid and electrolyte replacement therapy.

Treatment of diarrhoea with loperamide is only symptomatic.

Since persistent diarrhoea can be an indicator of potentially more serious conditions, loperamide should not be used for prolonged periods of time and the underlying cause of the diarrhoea should be investigated if clinical improvement is not observed within 48 hours of initiating treatment. Whenever an underlying etiology can be determined, specific treatment should be given when appropriate.

Although no pharmacokinetic data are available in patients with hepatic impairment, loperamide must be used with caution in these patients because of reduced first-pass metabolism (e.g. in cases of severe hepatic disturbance), as this might result in a relative overdose leading to CNS toxicity.

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

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.

Cardiac events including QT interval and QRS complex prolongation, 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.

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

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

4.5 Interaction with other medicinal products and other forms of interaction

Non-clinical and 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 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 (2 mg, up to 16 mg maximum daily dose), is unknown.

The concomitant administration of loperamide (4 mg single dose) and itraconazole, an inhibitor of CYP 3A4 and P-glycoprotein, resulted in a 3 to 4-fold increase in loperamide plasma concentrations. In the same study a CYP 2C8 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.

The concomitant administration of loperamide with oral desmopressin resulted in 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 Pregnancy and lactation

Pregnancy

Safety in human pregnancy has not been established, although studies in animals have not demonstrated any teratogenic or embryotoxic properties. As with other drugs, it is not advisable to administer loperamide in pregnancy, especially during the first trimester.

Breast-feeding

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

Women who are breast feeding infants should therefore be advised to consult their doctor for appropriate treatment.

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 loperamide. Therefore, it is advisable to use caution when driving a car or operating machinery. See section 4.8, Undesirable effects.

4.8 Undesirable effects

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 were in acute diarrhoea (N=2755) and 5 trials were in chronic diarrhoea (N=321).

The most commonly reported (i.e., ≥1% incidence) adverse reactions 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%).

Table 1 displays adverse reactions that have been reported with the use of loperamide hydrochloride from either clinical trials (in acute or chronic diarrhoea or both) 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 Reactions

System Organ Class	Adverse Reaction			
	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	

System Organ Class	Adverse Reaction			
	Common	**Uncommon**	**Rare**	**Not known**
Gastrointestinal Disorders	Constipation, Nausea, Flatulence	Abdominal pain, Abdominal discomfort, Dry mouth, Abdominal pain upper, Vomiting, Dyspepsia	Ileus (including paralytic ileus), Megacolon (including toxic megacolon – see section 4.4), Abdominal distension	Acute Pancreatitis
Skin and Subcutaneous Tissue Disorders		Rash	Bullous eruption (including Stevens Johnson syndrome, Toxic epidermal necrolysis and Erythema multiforme), Urticaria, Pruritus, Angioedema	
Renal and Urinary Disorders			Urinary retention	
General Disorders and Administration Site Conditions			Fatigue	

A number of the adverse reactions reported during the clinical investigations and post-marketing experience with loperamide hydrochloride 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.

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 reactions profile in this patient population was similar to that seen in clinical trials of loperamide hydrochloride 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 Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

In cases 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, torsades 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 the patient develops respiratory depression, airway obstruction, vomiting with impaired consciousness or other CNS symptoms of overdose, give naloxone urgently. Since the duration of action of loperamide is longer than that of naloxone (1 to 3 hours), repeated treatment with naloxone might be indicated, the patient should be kept under constant observation for at least 48 hours in order to detect any possible CNS depression. Other measures should be as indicated by the patient's clinical condition.

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. Loperamide increases the tone of the anal sphincter.

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 (40mg/kg/day – 240 times the maximum human use level) loperamide impaired fertility and foetal survival in association with maternal toxicity in rats. 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

Lactose monohydrate
Povidone
Crospovidone
Magnesium Stearate

6.2 Incompatibilities

None Known.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Blister Strip.
PVC: 250 micron, colourless.
Aluminium Foil: 25 micron.

3 such blister strips containing 10 tablets in an outer cardboard carton which also contains a Patient Information Leaflet.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Tillomed Laboratories Ltd
220 Butterfield
Great Marlings
Luton
LU2 8DL
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 11311/0016

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11/03/2009

10 DATE OF REVISION OF THE TEXT

01/10/2024