SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Loperamide Capsules 2 mg
Superdrug Acute Diarrhoea Relief Capsules
Asda Anti-Diarrhoea Capsules
Sainsbury's Anti-Diarrhoea Capsules Morrisons
Anti-Diarrhoea Capsules
Numark Anti-Diarrhoea Capsules
Tesco Diarrhoea relief Capsules
DiaFix Capsules
Vantage Anti-Diarrhoea Capsules
Co-op Diarrhoea Relief 2mg Capsules
Entrocalm Diarrhoea Relief 2mg Capsules
Galpharm Diarrhoea Relief 2mg Capsules
Spar Diarrhoea Relief 2mg Capsules
Sainsbury's Healthcare Anti-Diarrhoea 2mg Capsules
Optipharma Diarrhoea Relief 2mg Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Loperamide Hydrochloride BP 2mg

3. PHARMACEUTICAL FORM

Capsules for oral administration.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For symptomatic treatment of acute diarrhoea in adults, the elderly and adolescents over 12 years of age.

4.2 Posology and method of administration

Adults, the elderly and adolescents 12 years and over:

GSL status:

Two capsules to be taken initially, followed by one capsule after each loose motion, up to a maximum of six capsules in any 24 hours.

Not recommended for children under 12 years of age.

USE IN 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 4.4 Special warnings and special precautions for use).

When no clinical change is observed in the acute diarrhoea within 48 hours, the administration of loperamide must be interrupted and the patient must be advised to consult their doctor. Loperamide should not be used for more than 5 days without consulting a doctor.

Method of administration

Oral use.

The capsules should be taken with liquid

4.3 Contraindications

Patients with a known hypersensitivity to loperamide hydrochloride or to any of the excipients.

Children under 12 years of age

When inhibition of peristalsis is to be avoided due to the possible risk of significant sequelae including ileus, megacolon, toxic megacolon and certain poisonings, in particular:

- When ileus or constipation are present or when abdominal distension develops, particularly in severely dehydrated children.
- 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 hydrochloride 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

This medicine must be used with caution when the hepatic function necessary for the drug's metabolism is defective (e.g. in cases of severe hepatic disturbance), as this might result in a relative overdose leading to CNS toxicity.
Loperamide relieves the symptoms of diarrhoea only and is not a substitute for rehydration therapy. 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 particularly important in young children and in frail and elderly patients with acute diarrhoea.

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.
Loperamide hydrochloride should not be used in chronic diarrhoea, which requires follow-up by a physician.

GSL product: Use should not exceed 24 hours unless advised by a doctor. A doctor should be consulted if diarrhoea is still present after 24 hours treatment.

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 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 recommend duration of treatment.

Caution is needed in patients with a history of drug abuse. Abuse and misuse of loperamide, has been described (see section 4.9).
Loperamide is an opioid with low bioavailability and limited potential to penetrate the blood brain barrier at therapeutic doses. However, addiction is observed with opioids as a class

<u>Excipients</u>

This product contains 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

Non-clinical data have shown that loperamide is a P-glycoprotein substrate. Furthermore, loperamide is mainly metabolised by CYP3A4 and CYP2C8. Concomitant administration 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. The clinical relevance of this pharmacokinetic interaction with P-glycoprotein inhibitors, when loperamide is given at recommended dosages, is unknown.

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 Pregnancy and Lactation

Pregnancy
Safety in human pregnancy has not been established, although from animal studies there are no indications that loperamide HCl possesses any teratogenic or embryotoxic properties. As with other drugs, it is not advisable to administer this medicine in pregnancy, especially during the first trimester. Pregnant women may use loperamide following advice from a HCP.

Lactation
Small amounts of loperamide may appear in human breast milk. Therefore, this medicine is not recommended during breastfeeding.

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

Fertility
The results of animal studies do not indicate an effect of loperamide hydrochloride on fertility at therapeutic doses (see section 5.3). The effect on human fertility has not been evaluated.

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

4.8 Undesirable effects

Adults and adolescents 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 available data).

Table 1: Adverse Drug Reactions

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

General Disorders and Administration Site Conditions			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 (acute and chronic), including trials in children ≤ 12 years (N=3683).

b: See section 4.4 Special Warnings and Special Precautions for use.

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 (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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Symptoms:

In case of overdose (including relative overdose due to hepatic dysfunction), CNS depression (stupor, coordination abnormality, somnolence, miosis, muscular hypertonia, bradypnoea and respiratory depression), raised levels of pancreatic enzymes, 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:

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.

Gastric lavage may be recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antidiarrheals, intestinal anti-inflammatory / Anti-infective agents - 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.

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 – 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.
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

6.1. List of Excipients

Lactose BP
Maize starch BP
Talc BP
Magnesium stearate BP

Capsule shell is comprised of:
Gelatin BP
Quinoline Yellow (E104)
Erythrosine (E127)
Patent Blue (E131)
Titanium Dioxide (E171)

6.2. Incompatibilities

None.

6.3. Shelf Life

4 years.

6.4. Special Precautions for Storage

Store below 25°C in a dry place.

6.5 Nature and contents of container

Aluminium/PVC blister strips enclosed in an outer carton containing 2, 4 or 6 capsules.

Aluminium/ PVC/ PVDC blister strips enclosed in a cardboard outer containing 2, 4 or 6 capsules.

6.6. Instruction for Use, Handling and Disposal

Not applicable.

7. MARKETING AUTHORISATION HOLDER

Galpharm Healthcare Limited

Wrafton
Braunton
Devon
EX33 2DL
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 16028/0032

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17th July 1998

10 DATE OF REVISION OF THE TEXT

13/12/2024