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-operative Diarrhoea Relief 2mg Capsules
Entrocalm Diarrhoea Relief 2mg Capsules
Galpharm Diarrhoea Relief 2mg Capsules
Kirkland Signature Diarrhoea Relief 2mg Capsules
Dioraleze 2mg Capsules
Spar Diarrhoea Relief 2mg Capsules
Sainsbury's Healthcare Anti-Diarrhoea 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.

4.2 Posology and method of administration

Adults, the elderly and children over 12 years of age:

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.

P status:

Two capsules to be taken initially, followed by one capsule after each loose motion, up to a maximum of eight 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).

Method of administration

Oral use.

4.3 Contra-indications

Patients with acute ulcerative colitis or pseudomembranous colitis.

Patients with abdominal distension and where ileus and constipation are present.

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

Patients with bacterial enterocolitis.

Patients with acute dysentery characterised by blood in stools and elevated body temperatures.

Patients with inflammatory bowel disease.

Patients where inhibition of peristalsis is to be avoided due to the possible risk of significant sequelae including ileus, megacolon and toxic megacolon.

Children less than 12 years of age.

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.

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.

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.

P product: A doctor should be consulted if diarrhoea is still present after 24 hours treatment. Further investigation into the cause of diarrhoea should be considered if there is no improvement within 2 days of starting 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.

This product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp 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, 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.

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

Women who are pregnant or breastfeeding 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 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 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).

Table 1: Adverse Drug Reactions

System Organ Class	Indication		
	Common	**Uncommon**	**Rare**
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
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.

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.

5.1 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.

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.

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, 6, 8, 10, 12, 18, 24 or 30 capsules.

Aluminium / PVC/ PVdC blister strips enclosed in a cardboard outer containing 2, 4, 6, 8, 10, 12, 18, 24 or 30 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

20/09/2016