# 1 NAME OF THE MEDICINAL PRODUCT

Value Health Diarrhoea Relief 2mg Capsules

Boots Diarrhoea Relief 2mg Capsules

# 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

| | |
|---|---|
| Active ingredients | |
| Loperamide Hydrochloride | 2 mg per capsule |
| Excipients with known effect: | |
| Lactose monohydrate | 101.25 mg per capsule |
| Ponceau 4R E124 | |

For the full list of excipients, see section 6.1.

# 3 PHARMACEUTICAL FORM

Capsules, hard (Capsule)

Hard, gelatine capsule (size 4) with an opaque green cap printed "0611" in black ink, and an opaque grey body containing a white powder.

# 4 CLINICAL PARTICULARS

## 4.1 Therapeutic indications

P and GSL:

For the symptomatic treatment of acute diarrhoea, in adults and children 12 years and over.

For the symptomatic treatment of acute episodes of diarrhoea associated with irritable bowel syndrome in adults aged 18 years and over following initial diagnosis by a doctor.

## 4.2 Posology and method of administration

The capsules should be taken with liquid. For oral administration.

Acute diarrhoea:

Adults and children of 12 years of age and over:
The initial dose is 2 capsules (4 mg) followed by 1 capsule (2 mg) after every subsequent loose stool. The usual dose is 3-4 capsules (6 mg – 8 mg) a day. The maximum daily dose should not exceed 6 capsules (12 mg).

If symptoms persist for more than 24 hours consult your doctor.

For the symptomatic treatment of acute episodes of diarrhoea associated with irritable bowel syndrome in adults aged 18 years and over following initial diagnosis by a doctor:
Two capsules (4 mg) to be taken initially, followed by 1 capsule (2 mg) after every loose stool, or as previously advised by your doctor. The maximum daily dose should not exceed 6 capsules (12 mg).

Consult your doctor if you develop new symptoms, or if your symptoms worsen, or if your symptoms have not improved over two weeks.

Children under 12 years
Loperamide HCl capsules should not be used in children under 12 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 special precautions for use).

## 4.3 Contraindications

Loperamide HCl is contraindicated:

In patients with known hypersensitivity to loperamide HCl or to any of the excipients.

Loperamide HCl is contraindicated: :

- in children under 12 years of age.
- in patients with acute dysentery, which is characterised by blood in stools and high fever,
- 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 HCl should not be used when inhibition of peristalsis is to be avoided due to the possible risk of significant sequelae including ileus, megacolon and toxic megacolon. Loperamide HCl must be discontinued promptly when constipation, abdominal distension or ileus develop.

## 4.4 Special warnings and precautions for use

Treatment of diarrhoea with loperamide HCl is only symptomatic. Whenever an underlying aetiology can be determined, specific treatment should be given when appropriate.
In patients with diarrhoea, especially in children, frail and elderly patients, fluid and electrolyte depletion may occur. In such cases administration of appropriate fluid and electrolyte replacement therapy is the most important measure.

In acute diarrhoea**,** if clinical improvement is not observed within 48 hours, the administration of loperamide HCl should be discontinued and patients should be advised to consult their physician, since persistent diarrhoea can be an indicator of potentially more serious conditions. This medicine should not be used for prolonged periods until an underlying cause for persistent diarrhoea has been investigated and diagnosed by a doctor.

Patients with AIDS treated with loperamide HCl 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 HCl.

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. This medicine must be used with caution in patients with hepatic impairment as it may result in a relative overdose leading to CNS toxicity.

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

This medicine contains Ponceau 4R (E124) which can cause allergic-type reactions including asthma. Allergy is more common in those people who are allergic to aspirin.

If patients are taking this medicine to control episodes of diarrhoea associated with Irritable Bowel Syndrome previously diagnosed by their doctor, and clinical improvement is not observed within 48 hours, the administration of loperamide HCl should be discontinued and they should consult with their doctor. Patients should also return to their doctor if the pattern of their

symptoms changes or if the repeated episodes of diarrhoea continue for more than two weeks.

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.

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.

Warnings to be included in the leaflet:

<u>For acute diarrhoea</u>
If symptoms persist for more than 24 hours, consult your doctor.

<u>For acute episodes of diarrhoea associated with irritable bowel syndrome</u>
Only take loperamide HCl to treat acute episodes of diarrhoea associated with irritable bowel syndrome (IBS) if your doctor has previously diagnosed IBS.

If any of the following now apply, do not use the product without first consulting your doctor, even if you know you have IBS:

- If you are 40 years or over and it is some time since your last attack of IBS or the symptoms are different this time
- If you have recently passed blood from the bowel
- If you suffer from severe constipation
- If you are feeling sick or vomiting
- If you have lost your appetite or lost weight
- If you have difficulty or pain passing urine
- If you have a fever
- If you have recently travelled abroad

Consult your doctor if you develop new symptoms, or if your symptoms worsen, or if your symptoms have not improved over two weeks.

Keep all medicines out of the reach of children.

This medicine contains Ponceau 4R (E124) which can cause allergic-type reactions including asthma. Allergy is more common in those people who are allergic to aspirin.

This medicine 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 Interaction 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 doses, 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. The increase was not associated with increased pharmacodynamic effects as measured by pupillometry.

Concomitant treatment with oral desmopressin resulted in a 2-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

It is not advisable to administer this medicine in pregnancy. Women who are pregnant or breast feeding should therefore be advised to consult their doctor for appropriate treatment.

Although there is no indication that loperamide HCl possesses teratogenic or embryotoxic properties it should not be administered in pregnancy, especially during the first trimester.

Breast-feeding

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

Fertility

The effect on human fertility has not been evaluated.

## 4.7 Effects on ability to drive and to use machines

Loss of consciousness, depressed level of consciousness, tiredness, dizziness or drowsiness may occur in the setting of diarrhoeal syndromes treated with loperamide HCl. 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 (≥1/1000 to <1/100); rare (≥1/10,000 to <1/1000); very rare (<1/10,000); not known (cannot be estimated from the available data).

**Table 1 Adverse Drug Reactions**

| **System Organ Class** | **Indication** | | | |
|---|---|---|---|---|
| | Common | Uncommon | Rare | Not known |
| **Immune System Disorders** | | | Hypersensitivity reaction[a]<br>Anaphylactic reaction (including Anaphylactic shock)[a]<br>Anaphylactoid reaction[a] | |
| **Nervous System Disorders** | Headache | Dizziness<br>Somnolence[a] | Loss of consciousness[a]<br>Stupor[a]<br>Depressed level of consciousness[a]<br>Hypertonia[a]<br>Coordination abnormality[a] | |
| **Eye Disorders** | | | Miosis[a] | |

| | | | | |
|---|---|---|---|---|
| **Gastrointestinal Disorders** | Constipation<br>Nausea<br>Flatulence | Abdominal pain<br>Abdominal discomfort<br>Dry mouth<br>Abdominal pain upper<br>Vomiting<br>Dyspepsia[a] | Ileus[a] (including paralytic ileus)<br>Megacolon[a] (including toxic megacolon[b])<br>Abdominal distension | Acute pancreatitis |

| | | | | |
|---|---|---|---|---|
| **Skin and Subcutaneous Tissue Disorders** | | Rash | Bullous eruption[a] (including Stevens-Johnson syndrome, Toxic epidermal necrolysis and Erythema multiforme)<br>Angioedema[a]<br>Urticaria[a]<br>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 for 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 Special Precautions for use.

**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 case of overdose (including relative overdose due to hepatic dysfunction), CNS depression (stupor, coordination abnormality, somnolence, miosis, muscular hypertonia, and respiratory depression), urinary retention, constipation 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, 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.

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

Treatment

In cases of overdose, ECG monitoring for QT interval prolongation should be initiated.

If CNS 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.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1. Pharmacodynamic properties

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 diarrhoeal symptoms. Loperamide also increases the tone of the anal sphincter.

In a double blind randomised trial in 213 patients with acute diarrhoea, loperamide (56 patients) was compared with two other common antidiarrhoeal agents and placebo. Onset of antidiarrhoeal effect occurred as soon as one hour after intake of a 4mg dose of loperamide.

### 5.2. Pharmacokinetic properties

More than 65% of a dose of loperamide is reported to be absorbed from the gastrointestinal tract. The drug undergoes considerable first pass metabolism

in the liver and excretion via the bile in the faeces as the inactive conjugate. As a result of the drug's high affinity for the gut wall and its high first pass metabolism very little loperamide reaches the systemic circulation and therefore there is only a small amount of urinary excretion. The elimination half life is reported to be about 10 hours.

### 5.3 Preclinical safety data

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

Magnesium stearate

Maize starch (pregelatinised)

Hard gelatin capsule (gelatin, Ponceau 4R-E124, Indigo Carmine-E132, Titanium dioxide-E171, Yellow and black iron oxides E172)

Ink (Black iron oxide E172, Shellac, Propylene glycol)

### 6.2. Incompatibilities

Not applicable.

### 6.3 Shelf life

36 months

### 6.4. Special precautions for storage

Do not store above 30°C. Store in the original package.

### 6.5. Nature and contents of container

1. Blister of clear 250 micron PVC and 20 micron aluminium foil.
   Pack size: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 24, 28, 30, 32, 36, 48.

2. Blister of clear 250 micron PVC coated with 40 gsm PVdC and 20 micron aluminium foil.
   Pack size: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 24, 28, 30, 32, 36, 48.

### 6.6. Special precautions for disposal

Not applicable.

## 7 MARKETING AUTHORISATION HOLDER

The Boots Company PLC
1 Thane Road West
Nottingham
NG2 3AA

Trading as Value Health

## 8. MARKETING AUTHORISATION NUMBER

PL 00014/0611

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26/10/2005

## 10 DATE OF REVISION OF THE TEXT

12/07/2024