SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Loperamide Hydrochloride Capsules 2mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Loperamide hydrochloride 2mg

For excipients, see 6.1

Contains lactose 100mg per capsule

3. PHARMACEUTICAL FORM

Size 4, green opaque cap and a mauve opaque body, hard gelatin capsule marked “LOPERAMIDE 2” on the cap

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

POM:
Loperamide is indicated for the symptomatic treatment of acute diarrhoea of any aetiology including acute exacerbation of chronic diarrhoea for periods of up to 5 days, in adults and children over 4 years, and chronic diarrhoea in adults. Since persistent diarrhoea can be an indicator of potentially more serious conditions, loperamide should not be used for prolonged periods until the underlying cause of the diarrhoea has been investigated.

4.2 Posology and method of administration

Loperamide hydrochloride capsules 2mg are for oral administration. The capsules should be taken with liquid.

Acute diarrhoea:
Adults: two capsules initially, followed by 1 capsule after every loose stool, for up to 5 days. The usual dosage is 3 to 4 capsules a day; the maximum daily dose should not exceed 8 capsules.

Children:
9-12 years: the maximum dose is 1 capsule 4 times daily until diarrhoea is controlled, for up to 5 days.

4-8 years: Loperamide hydrochloride capsules 2mg cannot be divided and are therefore not recommended for use in children aged 4-8 years. A suitable alternative presentation of loperamide should be used in these patients.

If there is no improvement within 2 days of starting treatment further investigation of the cause of diarrhoea should be considered.

Chronic diarrhoea:

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Adults: studies have shown that patients may need widely differing amounts of loperamide hydrochloride. The starting dose should be between 2 and 4 capsules per day in divided doses, depending on severity. If required, this dose can be adjusted according to response. The maximum recommended daily dose is 8 capsules. Having established the patient’s daily maintenance dose, the capsules may be administered on a twice daily regimen. Tolerance has not been observed and therefore subsequent dosage adjustment should be unnecessary.

Children: loperamide is not recommended for treatment of chronic diarrhoea in children

Use in elderly: acute and chronic diarrhoea – as for adults

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 hydrochloride 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 is contraindicated:

- in patients with known hypersensitivity to loperamide hydrochloride or to any of the excipients
- in children aged less than 4 years

Loperamide should not be used as the primary therapy:

- in patients with acute dysentery which is characterised by blood in stools and elevated body temperature.
- 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 when inhibition of peristalsis is to be avoided due to the possible risk of significant sequelae including ileus, megacolon and toxic megacolon

Loperamide should be discontinued promptly when ileus or constipation are present or when abdominal distension develops, especially in severely dehydrated children.

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.

In patients with diarrhoea, especially in children, fluid and electrolyte depletion may occur. In such cases administration of appropriate fluid and electrolyte replacement therapy is the most important measure. Loperamide should not be given to children aged 2 to 6 years without medical prescription and supervision.

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 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 (viral or bacterial pathogens) treated with loperamide hydrochloride.

Although no pharmacokinetic data are available in patients with hepatic impairment, loperamide should be used with caution in such patients because of first pass metabolism. Patients with hepatic dysfunction should be monitored closely for signs of central nervous system (CNS) toxicity.

**Excipients**
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 Interaction with other medicinal products and other forms of interaction

**Effect of other medications on loperamide**

In vitro studies have shown that loperamide is metabolised by cytochrome P450 3A4 and 2C8 enzymes and is a substrate for P-glycoprotein.

Opioid–like central nervous system effects have been reported in volunteer studies with concomitant administration of loperamide (16 mg or 24 mg single dose) with quinidine (600mg or 800mg). Quinidine may increase penetration of loperamide into the brain due to inhibition of central P-glycoprotein. The clinical significance of the pharmacokinetic interaction with P-glycoprotein inhibitors when loperamide is given at recommended dosages (2mg, up to 16mg maximum daily dose) is unknown.

Concomitant administration of loperamide 16 mg and ritonavir, an inhibitor of both P-glycoprotein and CYP3A4, resulted in a two to three-fold increase in the AUC of loperamide but without evidence of enhanced central nervous system effect.

The concomitant administration of loperamide (4mg 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 increased pharmacodynamic effects as measured by psychomotor tests (i.e., subjective drowsiness and the Digit Symbol Substitution Test).

The concomitant administration of loperamide (16mg 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.

**Effect of loperamide on other medications**
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
Although there are no indications that loperamide possesses teratogenic or embryotoxic properties, the anticipated therapeutic benefits should be weighed against potential hazards before loperamide is given during pregnancy, especially during the first trimester.

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

4.7 Effects on ability to drive and use machines

Tiredness, dizziness or drowsiness may occur in the setting of diarrheal syndromes treated with Loperamide. Therefore, it is advisable to use caution when driving a car or operating machinery.

4.8 Undesirable effects

The safety of loperamide HCl was evaluated in 3076 adults and children aged ≥ 12 years who participated in 31 controlled and uncontrolled clinical trials of loperamide HCl 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 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%). In clinical trials in chronic diarrhoea, the most commonly reported (i.e. ≥1% incidence) ADRs were: flatulence (2.8%), constipation (2.2%), nausea (1.2%) and dizziness (1.2%).

Table 1 displays ADRs that have been reported with the use of loperamide HCl from either clinical trials (in acute or chronic diarrhea 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 <1/10,000); and very rare (<1/10,000).

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Acute diarrhoea (N=2755)</th>
<th>Chronic diarrhoea (N=321)</th>
<th>Acute + chronic diarrhoea and post-marketing experience</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immune system disorders</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hypersensitivity reaction&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>Rare</td>
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<tr>
<td>Anaphylactic reaction (including anaphylactic shock)&lt;sup&gt;a&lt;/sup&gt;</td>
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<td></td>
<td></td>
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<tr>
<td>Anaphylactoid reaction&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Nervous system disorders</strong></td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Headache</td>
<td>uncommon</td>
<td>Uncommon</td>
<td>Uncommon</td>
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<tr>
<td>Dizziness</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Somnolence&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss of consciousness&lt;sup&gt;a&lt;/sup&gt;, Stupor&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressed level of consciousness&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Hypertonia&lt;sup&gt;a&lt;/sup&gt;, co-ordination abnormality&lt;sup&gt;a&lt;/sup&gt;</td>
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</tbody>
</table>

**Eye disorders**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Acute diarrhoea (N=2755)</th>
<th>Chronic diarrhoea (N=321)</th>
<th>Acute + chronic diarrhoea and post-marketing experience</th>
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</thead>
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</table>

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<table>
<thead>
<tr>
<th>Miosis&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Rare</th>
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</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td><strong>Common</strong></td>
</tr>
<tr>
<td>Constipation, nausea, flatulence</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Abdominal pain, abdominal discomfort, dry mouth</td>
<td>Rare</td>
</tr>
<tr>
<td>Abdominal pain upper, vomiting</td>
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<tr>
<td>Dyspepsia</td>
<td></td>
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<tr>
<td>Ileus&lt;sup&gt;a&lt;/sup&gt; (including paralytic ileus)</td>
<td></td>
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<tr>
<td>Megacolon&lt;sup&gt;a&lt;/sup&gt; (including toxic megacolon&lt;sup&gt;b&lt;/sup&gt;), glossodynia&lt;sup&gt;a,c&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>Abdominal distension</td>
<td></td>
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<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td><strong>Common</strong></td>
</tr>
<tr>
<td>Rash</td>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td><strong>Rare</strong></td>
</tr>
<tr>
<td>Bullous eruption&lt;sup&gt;a&lt;/sup&gt; (including Stevens-Johnson syndrome), Toxic epidermal necrolysis and erythema multiforme), angioedema&lt;sup&gt;a&lt;/sup&gt;, Urticaria&lt;sup&gt;a&lt;/sup&gt;, Pruritus&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
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<tr>
<td><strong>Renal and Urinary disorders</strong></td>
<td><strong>Common</strong></td>
</tr>
<tr>
<td>Urinary retention&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td><strong>Common</strong></td>
</tr>
<tr>
<td>Fatigue&lt;sup&gt;a&lt;/sup&gt;</td>
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</tbody>
</table>

<sup>a</sup>: 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 in children ≤12years (N=3683).

<sup>b</sup>: See section 4.4 Special Warnings and Special Precautions for use.

<sup>c</sup>: Reported for the orodispersible tablet only.

For clinical trial ADRs where no frequency is presented the term was not observed or considered an ADR for this indication.

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**Paediatric population**

The safety of loperamide HCI was evaluated in 607 patients aged 10 days to 13 years who participated in 13 controlled and uncontrolled clinical trials of loperamide HCl used for the treatment of acute diarrhoea. In general, the ADR profile in this patient population was similar to that seen in clinical trials of loperamide HCl in adults and children aged 12 years and over.

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4.9 **Overdose**

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Large doses of Loperamide may cause features of opioid poisoning. The following patients should be referred for medical assessment:

- All patients who have taken a deliberate overdose
- All children
- Symptomatic adults
- Adults who have ingested 0.4mg/Kg of Loperamide or more.

Adults who have accidently ingested less than 0.4mg/Kg and who have no new symptoms since the time of ingestion should be advised to seek medical attention if symptoms develop. The effects of overdose will be potentiated by concurrent ingestion of alcohol and/or other centrally active drugs.

**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 and ileus may occur. If untreated deep coma and respiratory arrest can occur. Children, and patients with hepatic dysfunction, may be more sensitive to CNS effects.

Pin point pupils are often present but are not a reliable clinical sign. Their absence does not exclude opiate toxicity.

**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.

5. **PHARMACOLOGICAL PROPERTIES**

5.1 **Pharmacodynamic properties**

Loperamide inhibits peristalsis and is used in the treatment of some diarrhoeas. Studies remain to be done to show the value of loperamide in acute infective diarrhoea. It should not be used to treat young children.

Loperamide is also used in ileostomy management to control the volume in discharge.

5.2 **Pharmacokinetic properties**

Loperamide is incompletely absorbed from the gastrointestinal tract. Its elimination half-life is reported to range from 7 to 15 hours. It is mainly excreted in the faeces.

Loperamide probably accumulates in the wall of the small intestine and is released extremely slowly.

5.3 **Preclinical safety data**

No data of relevance to the prescriber, which is additional to that included in other sections of the SPC.

6. **PHARMACEUTICAL PARTICULARS**

6.1 **List of excipients**

Lactose monohydrate

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Maize starch
Magnesium stearate

Cap:
Quinoline yellow oxide (E104)
Indigo carmine (E132)
Titanium dioxide (E171)
Gelatin

Body:
Erythrosine (E127)
Indigo carmine (E132)
Black iron oxide (E172)
Titanium dioxide (E171)
Gelatin

6.2 Incompatibilities

None known

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 25°C

6.5 Nature and contents of container

White, opaque PVC 250µm/hard temper aluminium foil 25µm blister packs

Polypropylene pots with white polyethylene caps with optional use of polyethylene ullage fillers

POM:
Blister packaging: 4, 6, 8, 10, 12, 18, 20, 28, 30, 60, 250, 500
Polypropylene pots: 4, 6, 8, 10, 12, 18, 20, 28, 50, 100, 250, 500

P:
Blister packaging: 4, 6, 8, 10, 16, 18, 24, 30

Not all pack sizes may be marketed

6.6 Special precautions for disposal

No specific instructions for use/handling

7. MARKETING AUTHORISATION HOLDER

Co-pharma Ltd
Unit 4 Metro Centre
Tolpits Lane
Watford
Hertfordshire
Version 5, 30.07.2012
WD1 8SS

8. MARKETING AUTHORISATION NUMBER(S)

PL 13606/0045

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

July 2012

10. DATE OF REVISION OF THE TEXT

July 2012