Core Safety Profile

Active substance: Loperamide hydrochloride

P-RMS: PL/H/PSUR/0012/002
Date of FAR: 05.02.2014
4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Adults and Children 6-17 Years

Orodispersible tablets

The orodispersible tablet should be placed on the tongue. The tablet will dissolve and is to be swallowed with saliva. No liquid intake is needed for the orodispersible tablet.

Capsules, Tablets

The tablets and capsules should be taken with liquid.

Acute diarrhea: the initial dose is 2 capsules or tablets (4 mg) for adults and 1 capsule or tablet (2 mg) for children; followed by 1 capsule or tablet (2 mg) after every subsequent loose stool.

Chronic diarrhea: the initial dose is 2 capsules or tablets (4 mg) daily for adults and 1 capsule or tablet (2 mg) daily for children; this initial dose should be adjusted until 1-2 solid stools a day are obtained, which is usually achieved with a maintenance dose of 1-6 capsules or tablets (2 mg-12 mg) daily.

The maximum dose for acute and chronic diarrhea is 8 capsules or tablets (16 mg) daily for adults; in children it must be related to the body weight (3 capsules or tablets/20 kg) but should not exceed a maximum of 8 tablets per day.

Children 2 to 5 Years

The orodispersible tablet should not be used in children under 6 years of age.

Oral solution (2 mg/10 mL)

1 measuring cap (= 5 mL oral solution = 1 mg loperamide) per 10 kg body weight, 2 or 3 times daily. As soon as normal stools are passed or in the case no stools have been passed for more than 12 hours, the treatment with loperamide HCl must be discontinued.

The maximum daily dose is 3 measuring caps (= 15 mL oral solution = 3 mg loperamide) per 10 kg body weight.

Oral liquid (2 mg/15 mL)

1 measuring cup (= 7.5 mL oral liquid = 1 mg loperamide) per 10 kg body weight, 2 or 3 times daily. As soon as normal stools are passed or in the case no stools have been passed for more than 12 hours, the treatment with loperamide HCl must be discontinued.

The maximum daily dose is 3 measuring cups (= 22.5 mL oral solution = 3 mg loperamide) per 10 kg body weight.

Children Under 2 Years

Loperamide HCl should not be used in children under 2 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 a known hypersensitivity to loperamide HCl or to any of the excipients.
- Loperamide HCl should not be used in children under 2 years of age.
- The loperamide HCl orodispersible tablet should not be used in children under 6 years of age.
- Loperamide HCl should not be used as the primary therapy:
  - in patients with acute dysentery, which is characterized 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 special precautions for use

Treatment of diarrhea with loperamide HCl is only symptomatic. Whenever an underlying etiology can be determined, specific treatment should be given when appropriate.

In patients with diarrhea, 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 HCl should not be given to children aged 2 to 6 years of age without medical prescription and supervision.

In acute diarrhea, 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.
Patients with AIDS treated with loperamide HCl for diarrhea 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. Patients with hepatic dysfunction should be monitored closely for signs of central nervous system (CNS) toxicity.

Note: For OTC products, the last sentence in the above paragraph should be replaced with the following wording: This medicine must be used with caution in patients with hepatic impairment as it may result in a relative overdose leading to CNS toxicity.

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

Small amounts of loperamide may appear in human breast milk. Therefore, loperamide HCl is not recommended during breast-feeding.
Note: For OTC products, the last two paragraphs may be replaced with the following wording: 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.

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 HCl. Therefore, it is advisable to use caution when driving a car or operating machinery.

4.8 Adverse reactions

Adults and children aged ≥12 years

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 trial (in acute or chronic diarrhoea or both) or post-marketing experience.

The data in Table B represent the results from 3076 adults and children aged ≥12 years of age 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 frequency categories presented in Table B 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 A: Frequency of ADRs Reported with the Use of Loperamide HCl from Clinical Trials in Adults and Children Aged ≥ 12 Years of Age

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Indication</th>
<th></th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>Acute Diarrhoea (N=2755)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>Common</td>
<td></td>
<td></td>
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<tr>
<td>Dizziness</td>
<td>Uncommon</td>
<td></td>
<td></td>
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<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation, Nausea, Flatulence</td>
<td>Common</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain, Abdominal discomfort, Dry mouth</td>
<td>Uncommon</td>
<td></td>
<td></td>
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<tr>
<td>Abdominal pain upper, Vomiting</td>
<td>Uncommon</td>
<td></td>
<td></td>
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<tr>
<td>Dyspepsia</td>
<td>Uncommon</td>
<td></td>
<td></td>
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<tr>
<td>Abdominal distension</td>
<td>Rare</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>Uncommon</td>
<td></td>
<td></td>
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</tbody>
</table>

Loperamide HCl Post-Marketing ADR Data

The process for determining post-marketing ADRs for loperamide HCl did not differentiate between chronic and acute diarrhoea indications or differentiate between adults or children; therefore, the ADRs listed below represents the combined indications and subject populations. The ADRs identified during post-marketing for loperamide HCl are listed below by System Organ Class and Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term (PT):

**Immune System Disorders:** Hypersensitivity reaction, Anaphylactic reaction (including Anaphylactic shock), and Anaphylactoid reaction.

**Nervous System Disorders:** Somnolence, Loss of consciousness, Stupor, Depressed level of consciousness, Hypertonia, and Coordination abnormality.

**Eye Disorders:** Miosis.

**Gastrointestinal Disorders:** Ileus (including Paralytic ileus), Megacolon (including Toxic megacolon), and Glossodynia.

**Skin and Subcutaneous Tissue Disorders:** Bullous eruption (including Stevens-Johnson syndrome, Toxie epidermal necrolysis and Erythema multiforme), Angioedema, Urticaria, and Pruritus.

**Renal and Urinary Disorder:** Urinary retention.

**General Disorders and Administration Site Conditions:** Fatigue.

*Paediatric population*
The safety of loperamide HCl 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.

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 and ileus may occur. Children may be more sensitive to CNS effects than adults.

**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.