PROFESSIONAL INFORMATION FOR

CIPLA LOPERAMIDE

SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

CIPLA LOPERAMIDE (2 mg, tablets)

WARNING: Torsades de Pointes and Sudden Death

- **Cases of Torsades de Pointes, cardiac arrest and death have been reported with the use of a higher than recommended dosage of CIPLA LOPERAMIDE (see section 4.4 and section 4.9).**
- **CIPLA LOPERAMIDE is contraindicated in paediatric patients under 2 years of age (see section 4.3).**
- **Avoid higher than recommended dosages of CIPLA LOPERAMIDE in adults and paediatric patients 2 years and older, due to the risk of serious cardiac adverse reactions (see section 4.2).**

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 mg loperamide hydrochloride.

Contains sugar: lactose monohydrate 100 mg per tablet.

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

Tablets

Light green coloured, capsule-shaped, biconvex, uncoated tablets, plain on one side and a break line on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults and children 6 years and older

CIPLA LOPERAMIDE is indicated for the following:

- Symptomatic relief and control of acute and chronic non-specific diarrhoea.
- Inhibition of peristalsis and slowing of intestinal transit time in patients with ileostomies, colostomies and other intestinal resections.

Children younger than 6 years

- CIPLA LOPERAMIDE is indicated for inhibition of peristalsis and slowing of intestinal transit time.

4.2 Posology and method of administration

Posology

CIPLA LOPERAMIDE should not be taken by children younger than 2 years. CIPLA LOPERAMIDE tablets, however, are not suitable for children under 6 years of age.

Acute non-specific diarrhoea

Adults and children of 6 years and older

Adults: 2 tablets (4 mg) initially, followed by 1 tablet (2 mg) after each subsequent loose stool.

Children: 1 tablet (2 mg) initially, followed by 1 tablet (2 mg) after each subsequent loose stool.

The following maximum daily doses should not be exceeded:

Bodyweight (kg)	Maximum Daily Dose
14 to 19 kg	2 tablets (4 mg)
20 to 26 kg	3 tablets (6 mg)
27 to 33 kg	4 tablets (8 mg)
34 to 39 kg	5 tablets (10 mg)
40 to 46 kg	6 tablets (12 mg)
47 to 53 kg	7 tablets (14 mg)
≥ 54 kg	8 tablets (16 mg)

Important: CIPLA LOPERAMIDE must be STOPPED as soon as diarrhoea is under control. Patients with acute diarrhoea, showing no improvement within 48 hours, should discontinue CIPLA LOPERAMIDE and consult their doctor.

Chronic non-specific diarrhoea (a doctor must be consulted)

A virtually normal bowel movement is usually obtained with individually adjusted dosages.

Initial dose: 2 tablets (4 mg) daily for adults and 1 tablet (2 mg) daily for children 6 years and older.

The initial dose should be adjusted until 1 to 2 solid stools per day are obtained. This is normally achieved on a maintenance dose of 1 to 6 tablets (2 to 12 mg) per day.

The dosage should be decreased if constipation occurs.

Special populations

Elderly

No dose adjustment is necessary.

In general, elderly patients may be more susceptible to medicine-associated effects of the QT interval. CIPLA LOPERAMIDE should be avoided in elderly patients taking medicines that can result in prolongation of the QT interval (for example, Class IA or III antidysrhythmics) or in patients with risk factors for Torsades de Pointes (see **section 4.4**).

Hepatic impairment

There is no pharmacokinetic data on patients with hepatic impairment. However, because of reduced first pass metabolism, CIPLA LOPERAMIDE should be used with caution in such patients (see **section 4.4**).

4.3 Contraindications

CIPLA LOPERAMIDE is contraindicated in:

- Patients with a known hypersensitivity to loperamide hydrochloride or to any of the excipients in CIPLA LOPERAMIDE (see **section 6.1**).
- Infants younger than 2 years, due to the risk of respiratory depression and serious cardiac adverse reactions (see **section 4.4**).
- Patients with abdominal pain in the absence of diarrhoea.
- Patients with acute dysentery, characterised by a high fever and blood in the stools, where it should not be used as primary therapy.
- Patients with acute ulcerative colitis.
- Patients with bacterial enterocolitis resulting from invasive infections, including those caused by *Salmonella*, *Shigella* and *Campylobacter*.
- Patients with pseudomembranous colitis (e.g. *Clostridium difficile*) associated with broad-spectrum antibiotic use.
- Patients with ileus (see **section 4.4**).

4.4 Special warnings and precautions for use

Cardiac adverse reactions, including Torsades de Pointes and sudden death

Cases of prolongation of the QT/QTc interval, Torsades de Pointes, other ventricular dysrhythmias, cardiac arrest, some resulting in death, have been reported in adults with use of higher than recommended doses per day of CIPLA LOPERAMIDE. Cases include patients who were abusing or misusing loperamide hydrochloride, as in CIPLA LOPERAMIDE (see **"Abuse"** and **"Dependence"** below, and **section 4.9**). Cases of syncope and ventricular tachycardia have been reported in adult patients receiving the recommended dosage of CIPLA LOPERAMIDE. Some of these patients were taking other medicines or had other risk factors that may have increased their risk of cardiac adverse reactions. Additionally, postmarketing cases of cardiac arrest, syncope, and respiratory depression have been reported in paediatric patients less than 2 years of age.

CIPLA LOPERAMIDE is contraindicated in paediatric patients less than 2 years of age due to the risks of respiratory depression and serious cardiac adverse reactions. Higher than recommended dosages of CIPLA LOPERAMIDE should be avoided in adults and paediatric patients 2 years of age and older, due to the risk of serious cardiac adverse reactions (see **section 4.2** and **section 4.9**).

Avoid CIPLA LOPERAMIDE in:

- Combination with other medicines or herbal products that are known to prolong the QT interval, including Class 1A (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antidysrhythmics, antipsychotics (e.g. chlorpromazine, haloperidol, thioridazine, ziprasidone), antibiotics (e.g. moxifloxacin), or any other medicine known to prolong the QT interval (e.g. pentamidine, levomethadyl acetate, methadone).
- Patients with risk factors for QT prolongation, including patients with congenital long QT syndrome, with a history of cardiac dysrhythmias or other cardiac conditions, elderly patients and those with electrolyte abnormalities.

Dehydration

Fluid and electrolyte depletion may occur in patients with diarrhoea, especially in infants and in frail and elderly patients. In such cases, appropriate fluid and electrolyte replacement (oral rehydration therapy [ORT]) is the most important priority. The use of CIPLA LOPERAMIDE does not preclude the need for appropriate fluid and electrolyte therapy.

Gastrointestinal disorders

Generally, the use of CIPLA LOPERAMIDE should be avoided when inhibition of peristalsis could possibly increase the risk of significant sequelae, including ileus, megacolon and toxic megacolon. CIPLA LOPERAMIDE must be discontinued immediately when abdominal distension, ileus or constipation develops.

CIPLA LOPERAMIDE treatment gives symptomatic relief of diarrhoea only. Specific treatment, if appropriate or when indicated, is recommended whenever an underlying aetiology can be determined.

Patients with AIDS-associated diarrhoea that are treated with CIPLA LOPERAMIDE should have treatment stopped at the earliest signs of abdominal distension. Toxic megacolon has been reported in AIDS patients with infectious colitis from both viral and bacterial pathogens treated with CIPLA LOPERAMIDE.

Persistent diarrhoea may potentially be an indicator of more serious conditions, therefore CIPLA LOPERAMIDE should not be used for extended periods until the underlying cause has been investigated.

If clinical improvement of acute diarrhoea does not occur within 48 hours, treatment with CIPLA LOPERAMIDE should be stopped and patients should be advised to consult their doctor.

Paediatric population

CIPLA LOPERAMIDE should not be administered to children less than 6 years of age without a medical prescription and proper supervision. It should be used with special caution in paediatric patients because of the greater variability of response in this age group. Dehydration, particularly in paediatric patients less than 6 years of age, may further influence the variability of response to CIPLA LOPERAMIDE. CIPLA LOPERAMIDE is not recommended for routine use in acute or chronic diarrhoea in children less than 6 years of age.

CIPLA LOPERAMIDE is contraindicated in paediatric patients younger than 2 years of age due to the risks of respiratory depression and serious cardiac adverse reactions (see **section 4.3**).

Postmarketing cases of cardiac arrest, syncope, and respiratory depression have been reported in paediatric patients less than 2 years of age. Paediatric patients may be more sensitive to CNS effects, such as altered mental status, somnolence, and respiratory depression, than adults. There have been reports of paralytic ileus associated with abdominal distention. Most of these reports occurred in the setting of acute dysentery, overdose, and with paediatric patients less than two years of age.

The safety and efficacy of CIPLA LOPERAMIDE in paediatric patients with chronic diarrhoea have not been established.

In case of accidental overdosage of CIPLA LOPERAMIDE by paediatric patients, see **section 4.9** for suggested treatment.

Allergic reactions

Allergic reactions including anaphylaxis and anaphylactic shock have been reported (see **section 4.8**).

Hepatic impairment

There is no pharmacokinetic data on patients with hepatic impairment. However, because of reduced first pass metabolism, CIPLA LOPERAMIDE should be used with caution in such patients. Patients with hepatic dysfunction should be closely observed for symptoms of central nervous system toxicity.

Renal impairment

No pharmacokinetic data are available in patients with renal impairment. Since CIPLA LOPERAMIDE is largely metabolised, and excreted mainly in the faeces as metabolites or unchanged medicine, dosage adjustments in patients with renal impairment are not required.

Geriatric use

No pharmacokinetic data are available in elderly patients. However, no major differences have been reported in CIPLA LOPERAMIDE disposition in elderly patients with diarrhoea, relative to young patients.

In general, elderly patients may be more susceptible to medicine-associated effects on the QT interval. CIPLA LOPERAMIDE should be avoided in elderly patients taking medicines that can result in prolongation of the QT interval (for example, Class IA or III antidysrhythmics) or in patients with risk factors for Torsades de Pointes.

Abuse

CIPLA LOPERAMIDE is a mu-opioid agonist. Loperamide abuse and misuse have been reported, especially at doses of 60 mg or greater. CIPLA LOPERAMIDE can have greater CNS opioid effects at higher doses or with co-administration of medicines that increase systemic exposure and/or increase CNS penetration of loperamide (through inhibition of the

CYP450 enzyme system or inhibition of P-glycoprotein). CIPLA LOPERAMIDE is primarily misused for relief from opioid withdrawal and abused by a few users who obtain some (reportedly mild-moderate) level of euphoria.

Dependence

In animals, parenteral administration of loperamide hydrochloride, as in CIPLA LOPERAMIDE, can cause physical dependence, cross-tolerance to opioids, and all the other pharmacologic effects typical of mu-opioid agonists.

In morphine-dependent monkeys, loperamide hydrochloride at doses above those recommended for humans, prevented signs of morphine withdrawal.

Lactose

CIPLA LOPERAMIDE contains lactose. Patients with the rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption or fructose intolerance should not take CIPLA LOPERAMIDE.

4.5 Interaction with other medicines and other forms of interaction

Effects of other medicines on CIPLA LOPERAMIDE

Concomitant use of CIPLA LOPERAMIDE with inhibitors of CYP3A4 (e.g. itraconazole) or CYP2C8 (e.g. gemfibrozil) or inhibitors of P-glycoprotein (e.g. quinidine, ritonavir) can increase exposure to loperamide. The increased systemic exposure to loperamide may increase a risk for cardiac adverse reactions especially in patients who are taking multiple CYP-enzyme inhibitors, or in patients with underlying cardiac conditions (see **section 4.4**). Patients should be monitored for cardiac adverse reactions.

CYP3A4 inhibitors

Itraconazole

The co-administration of a single 4 mg dose of CIPLA LOPERAMIDE and itraconazole, an inhibitor of CYP3A4 and P-glycoprotein, results in a 3 to 4-fold increase in CIPLA LOPERAMIDE plasma levels.

CYP2C8 inhibitors

Gemfibrozil

The co-administration of a single 4 mg dose of CIPLA LOPERAMIDE and gemfibrozil, a CYP2C8 inhibitor, increases CIPLA LOPERAMIDE levels about 2-fold.

CYP3A4 and CYP2C8 inhibitors

The co-administration of a single 4 mg dose of CIPLA LOPERAMIDE and the combination of itraconazole and gemfibrozil, results in a 4-fold increase in CIPLA LOPERAMIDE peak plasma concentrations and a 13-fold increase in total plasma exposure, however these increases are not associated with central nervous system (CNS) effects.

P-glycoprotein inhibitors

According to non-clinical data CIPLA LOPERAMIDE is a P-glycoprotein substrate. Concomitant administration of a single 16 mg dose of CIPLA LOPERAMIDE with quinidine or ritonavir, both P-glycoprotein inhibitors, results in a 2 to 3-fold increase in CIPLA LOPERAMIDE plasma concentration when co-administered with quinidine, but not with ritonavir. Respiratory suppression may occur. Due to the potential for enhanced CNS adverse reactions, caution should be exercised when CIPLA LOPERAMIDE is administered at the recommended dosages (2 mg up to 16 mg maximum daily dose) with P-glycoprotein inhibitors.

The co-administration of a single 16 mg dose of CIPLA LOPERAMIDE and ketoconazole, an inhibitor of CYP3A4 and P-glycoprotein, results in a 5-fold increase in CIPLA LOPERAMIDE plasma levels. This increase is not associated with increased pharmacodynamic effects.

Co-administration of oral desmopressin results in a 3-fold increase of desmopressin plasma levels, apparently due to slower gastrointestinal motility.

It is anticipated that medicines with similar pharmacological properties may potentiate the effects of CIPLA LOPERAMIDE and that medicines that speed up gastrointestinal transit may decrease its effect.

Effects of CIPLA LOPERAMIDE on other medicines

Saquinavir

When a single 16 mg dose of CIPLA LOPERAMIDE is co-administered with a 600 mg single dose of saquinavir, CIPLA LOPERAMIDE decreases saquinavir exposure by 54 %, which may be of clinical relevance due to reduction of therapeutic efficacy of saquinavir. The effect of saquinavir on CIPLA LOPERAMIDE is of less clinical significance. Therefore, when CIPLA LOPERAMIDE is given with saquinavir, the therapeutic efficacy of saquinavir should be closely monitored.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of CIPLA LOPERAMIDE during pregnancy and lactation has not been established.

Breastfeeding

As small amounts of loperamide may appear in human breast milk, CIPLA LOPERAMIDE should not be taken when breastfeeding.

Fertility

The effect on human fertility has not been evaluated.

4.7 Effects on ability to drive and use machines

Caution should be used when driving a car or operating machinery during treatment of diarrhoeal syndromes with CIPLA LOPERAMIDE, as loss of consciousness, depressed level of consciousness, tiredness, dizziness or drowsiness may occur (see **section 4.8**).

4.8 Undesirable effects

a) Summary of the safety profile

The most frequently reported adverse reactions in patients with acute diarrhoea were constipation, flatulence, headache and nausea. In patients with chronic diarrhoea, the most commonly reported adverse reactions were flatulence, constipation, nausea and dizziness.

b) Tabulated list of adverse reactions

Adverse events in patients with acute diarrhoea

MedDRA system organ class	**Frequency**	**Side effects**
Nervous system disorders	*Frequent:*	Headache.
	Less frequent:	Dizziness.
Gastrointestinal disorders	*Frequent:*	Constipation, flatulence, dry mouth, abdominal cramp, colic, nausea.
	Less frequent:	Abdominal pain, abdominal discomfort, upper abdominal pain, abdominal distension, vomiting (see **section 4.4**).
Skin and subcutaneous tissue disorders	*Less frequent*:	Rash.

Adverse events in patients with chronic diarrhoea

MedDRA system organ class	**Frequency**	**Side effects**
Nervous system disorders	*Frequent:*	Dizziness, headache.
Gastrointestinal disorders	*Frequent:*	Constipation, nausea, vomiting, headache, meteorism, abdominal pain, abdominal cramp, colic, flatulence.
	Less frequent:	Dry mouth, abdominal discomfort, dyspepsia.

Adverse events in patients with acute or chronic diarrhoea

MedDRA system organ class	**Frequency**	**Side effects**
Gastrointestinal disorders	*Frequent:*	Nausea, constipation, abdominal cramp.

Adverse event in paediatric patients (under 12 years) with acute diarrhoea

MedDRA system organ class	**Frequency**	**Side effects**
Nervous system disorders	*Less frequent:*	Somnolence, dizziness, headache.
Gastrointestinal disorders	*Frequent:*	Vomiting.
	Less frequent:	Nausea, abdominal pain, constipation.
Skin and subcutaneous tissue disorders	*Less frequent:*	Rash.

Postmarketing

MedDRA system organ class	**Frequency**	**Side effects**
Immune system disorders	*Less frequent:*	Allergic reactions, severe hypersensitivity reactions including anaphylactic shock and anaphylactoid reactions.
Psychiatric disorders	*Less frequent:*	Drowsiness.
Nervous system disorders	*Less frequent:*	Dizziness, somnolence, loss of consciousness, stupor, depressed level of consciousness, hypertonia, coordination abnormality.
Eye disorders	*Less frequent:*	Miosis.
Cardiac disorders	*Frequency unknown*:	QT/QTc interval prolongation, Torsades de Pointes, other ventricular dysrhythmias, cardiac arrest, syncope, and death (see **section 4.4** and **section 4.9**).
Gastrointestinal disorders	*Less frequent:*	Ileus (including paralytic ileus), megacolon including toxic megacolon, glossodynia.
	Frequency unknown:	Dry mouth, abdominal pain, distention or discomfort, nausea, vomiting, flatulence, dyspepsia, constipation, (see **section 4.3** and **section 4.4**), acute pancreatitis.
Skin and subcutaneous tissue disorders	*Less frequent:*	Rash, pruritus, urticaria, angioedema, bullous eruptions, including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis.
Renal and urinary disorders	*Less frequent:*	Urinary retention.

General disorders and administration site conditions	*Less frequent:*	Tiredness, fatigue.

c) Description of selected adverse reactions

A number of the adverse events experience with CIPLA LOPERAMIDE are also frequent symptoms of the underlying diarrheal syndrome (abdominal pain/discomfort, nausea, vomiting, dry mouth, tiredness, drowsiness, dizziness, constipation, and flatulence). These symptoms may be difficult to distinguish from undesirable medicine effects. An increased risk of abdominal pain, including pancreatitis has been reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA website, or to Cipla Medpro (Pty) Ltd. by email: drugsafetysa@cipla.com or telephone: 080 222 6662 (toll free).

4.9 Overdose

The use of higher than recommended CIPLA LOPERAMIDE doses may result in life-threatening cardiac, CNS and respiratory adverse reactions. Children may be more sensitive to central nervous system effects of loperamide than adults.

If over-exposure occurs, the patient must report to their doctor or hospital for current information on the management of poisoning or overdosage.

Cardiac effects

Symptoms

Cases of overdosage with CIPLA LOPERAMIDE (chronic ingestion of doses ranging from 70 mg to 1600 mg daily; 4 to 100 times the recommended dose) have resulted in life-threatening cardiac adverse reactions, including QT/QTc and QRS interval prolongation, Torsades de Pointes, Brugada syndrome and other ventricular dysrhythmias, syncope, cardiac arrest, and death. Cases include patients who were abusing (using supratherapeutic doses in place of opioids to induce euphoria) or misusing CIPLA LOPERAMIDE (taking higher than recommended doses to control diarrhoea or to prevent opioid withdrawal).

Management

Consider CIPLA LOPERAMIDE as a possible cause of cardiac dysrhythmias in patients who may have a history of opioid abuse or recent ingestion of unknown medicines and in the differential diagnosis of unstable dysrhythmias, prolonged QTc or QRS intervals, and Torsades de Pointes.

If CIPLA LOPERAMIDE-induced cardiac toxicity is suspected, it should be discontinued promptly and therapy to manage and prevent cardiac dysrhythmias and serious outcomes should be initiated.

In many cases of CIPLA LOPERAMIDE overdosage, antidysrhythmic medications (e.g. magnesium sulfate) were ineffective in resolving the dysrhythmias and preventing further episodes of Torsades de Pointes. Electrical cardioversion and overdrive pacing, and isoproterenol continuous infusion were reported to manage QTc prolongation in the setting of overdose.

Laboratory testing

CIPLA LOPERAMIDE serum concentrations are not widely available or clinically useful to guide patient management.

CNS and respiratory depression

Symptoms

An overdose (including a relative overdose due to hepatic dysfunction) may result in opioid toxic effects, including central nervous system depression (e.g. altered mental status, coordination abnormality, stupor, miosis, somnolence, muscular hypertonia and respiratory depression), constipation, hypotension, paralytic ileus and urinary retention. Children and patients with hepatic dysfunction seem to be more sensitive to the neurological side effects of CIPLA LOPERAMIDE, including respiratory depression. Convulsions have been reported in children younger than 2 years.

Excessive inhibition of peristaltic movements, nausea and a dry mouth.

Management

Symptomatic and supportive treatment is recommended. CIPLA LOPERAMIDE non-cardiac dysrhythmia overdosages should be treated as opioid overdosages. An antidote, such as naloxone, can be administered to reverse the opioid-related toxicity, including CNS and respiratory depression, and hypotension associated with CIPLA LOPERAMIDE overdosage.

In adults and paediatric patients, naloxone may be administered intravenously. Appropriate doses of naloxone, via intranasal, intramuscular, intraosseous, or subcutaneous administration may be necessary if the intravenous route is not available. If the desired degree of opioid related toxicity counteraction and improvement are not obtained, naloxone may be repeated at two- to three-minute intervals. Repeated treatment with naloxone may be indicated, as the duration of action of CIPLA LOPERAMIDE is longer than that of naloxone (1 to 3 hours). The patient should therefore be closely monitored for at least 48 hours to detect possible central nervous system depression.

If no response in opioid-related effects is observed after naloxone has been administered, then diagnosis of opioid-induced toxicity should be questioned.

Refer to the naloxone prescribing information for complete information on initial and subsequent dosages.

For patients whose adverse reactions are responsive to naloxone, their vital signs, neurologic and cardiopulmonary status should be monitored for recurrence of opioid overdose symptoms for at least 24 hours after the last dose of naloxone, due to the prolonged intestinal retention of CIPLA LOPERAMIDE and the short duration (one to three hours) of naloxone. Patients with severe CNS or respiratory depression, and those who require multiple doses of naloxone to reverse symptoms, should be admitted to the hospital and may require intensive care.

Laboratory testing

Standard drug screens for opioids do not include an assay for CIPLA LOPERAMIDE; such testing for opioids will yield negative results, even in the presence of loperamide.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A.11.9 Antidiarrhoeals.

Pharmacotherapeutic group: Medicines acting on gastrointestinal tract.

ATC code: A07DA03.

Mechanism of action

Loperamide acts directly on the bowel wall by binding to the opiate receptor, thereby inhibiting hypermotility, increasing intestinal transit time and enhancing resorption of water and electrolytes. It inhibits peristalsis by decreasing the activity of both the longitudinal muscles (preparatory and reflex phases) and the circular muscles (reflex phase). Loperamide increases the tone of the anal sphincter, which helps reduce faecal incontinence and urgency.

Pharmacodynamic effects

These actions of loperamide result in the normalisation of stool in both acute and chronic diarrhoea. Onset of antidiarrhoeal action is observed within one hour following a single 4 mg dose of loperamide.

5.2 Pharmacokinetic properties

Absorption

Loperamide is not completely absorbed from the gut. It is extensively metabolised in the liver, therefore, systemic bioavailability is low.

Distribution

Loperamide shows a high affinity for binding to the gut wall in rats, with a preference for binding to receptors of the longitudinal muscle layer. Plasma protein binding is 95 %, primarily to albumin. Non-clinical data have indicated that loperamide is a P-glycoprotein substrate.

Biotransformation

Loperamide is nearly completely extracted by the liver, where it is largely metabolised, conjugated and excreted via the bile as conjugated loperamide. The main metabolic pathway for loperamide is oxidative *N*-demethylation, which is mediated primarily through CYP3A4 and CYP2C8. Due to this very high first pass effect, plasma levels of unchanged loperamide are very low.

Elimination

The half-life of loperamide is about 11 hours, ranging from 9 to 14 hours. Elimination of unchanged loperamide and its metabolites is mainly via the faeces.

Paediatric population

No pharmacokinetic studies were performed in the paediatric population. It is expected that pharmacokinetic behaviour of loperamide and interactions with loperamide will be similar to those in adults.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

anhydrous colloidal silica

brilliant blue

lactose monohydrate

magnesium stearate

maize starch

polyvinyl pyrrolidone

quinoline yellow

sodium starch glycollate

talc.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light and moisture.

Keep the blister strips in the outer carton until required for use.

6.5 Nature and contents of container

CIPLA LOPERAMIDE is packed in an aluminium foil and PVC/PVDC film blister strips of 6 and 8 tablets packed in 6's, 8's and 12's (2 x 6 in a carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD.

Building 9

Parc du Cap

Mispel Street

Bellville

7530

Customer Care: 080 222 6662

8. REGISTRATION NUMBER(S)

A39/11.9/0407

Namibia: NS1 10/11.9.2/0518

Botswana: S2 BOT1302401

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

First authorisation: 25 November 2005

Latest renewal: Not applicable.

10. DATE OF REVISION OF THE TEXT

29 October 2024