1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

DISCHEM ANTI-DIARRHOEAL TABLETS 2 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of DISCHEM ANTI-DIARRHOEAL TABLETS contains 2 mg of loperamide hydrochloride.

Contains sugar: Mannitol 80 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

DISCHEM ANTI-DIARRHOEAL TABLETS is a flat, white, bevelled edged tablet bisected on one side.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Adults and children 6 years and older:

DISCHEM ANTI-DIARRHOEAL TABLETS is indicated for:

- the control and symptomatic relief of acute and chronic non-specific diarrhoea.

- Inhibition of peristalsis and slowing intestinal transit time in patients with ileostomies, colostomies and other intestinal resections.

4.2. Posology and method of administration

Posology

DISCHEM ANTI-DIARRHOEAL tablets should not be administered to children under 6 years of age.

Acute non-specific diarrhoea

Adults and children 6 years and older: The usual initial dose of DISCHEM ANTI-DIARRHOEAL TABLETS is two tablets (4 mg) for adults, or 1 tablet (2 mg) for children as an initial dose followed by one tablet (2 mg) after each loose stool.

In acute diarrhoea, if clinical improvement is not observed within 48 hours, the administration of DISCHEM ANTI-DIARRHOEAL TABLETS should be discontinued, and patients should be advised to consult their doctor.

Do not exceed the following maximum daily dosages.

WEIGHT IN KILOGRAMS (kg)	**MAXIMUM DAILY DOSE**
From 14 kg	2 tablets (4 mg)
From 20 kg	3 tablets (6 mg)
From 27 kg	4 tablets (8 mg)
From 34 kg	5 tablets (10 mg)
From 40 kg	6 tablets (12 mg)
From 47 kg	7 tablets (14 mg)

From 54 kg	8 tablets (16 mg)

Important: Stop DISCHEM ANTI-DIARRHOEAL TABLETS as soon as diarrhoea is under control

Chronic non-specific diarrhoea (consult your doctor)

With individually adjusted dosage it is usually possible to obtain a virtually normal bowel movement.

The initial dose is 2 tablets (4 mg) daily for adults and 1 tablet (2 mg) daily for children of 6 years and over.

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

If constipation occurs, the dosage should be decreased.

Special populations

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, DISCHEM ANTI-DIARRHOEAL TABLETS should not be used in such patients because of reduced first pass metabolism (see section 4.3).

Method of administration

For oral administration.

4.3. Contraindications

DISCHEM ANTI-DIARRHOEAL TABLETS is contraindicated in:

- Patients with hypersensitivity to loperamide hydrochloride or to any excipients in DISCHEM ANTI-DIARRHOEAL TABLETS (see section 6.1).
- Should not be used as the primary therapy in patients with acute dysentery, which is characterised by blood in stools and high fever.
- In the treatment of acute infective diarrhoea.
- Patients with acute ulcerative colitis.
- Patients with bacterial enterocolitis caused by invasive organisms including *Salmonella, Shigella,* and *Campylobacter*.
- Patients with pseudomembranous colitis associated with the use of broad-spectrum antibiotics.
- Hepatic dysfunction as this may result in relative overdosing (see section 4.2).
- Patients whom inhibition of peristalsis must be avoided, due to the possible risk of significant sequelae including ileus, megacolon and toxic megacolon.
- Where constipation is present.
- Patients with inflammatory bowel disease.
- Pregnancy as safety has not been established.
- Children under 6 years.

DISCHEM ANTI-DIARRHOEAL TABLETS must be discontinued promptly when constipation, abdominal distension or ileus develop.

4.4. Special warnings and precautions for use

Treatment of diarrhoea with DISCHEM ANTI-DIARRHOEAL TABLETS are only symptomatic. Whenever an underlying aetiology can be determined, specific treatment should be given when appropriate (or when indicated).

Acute diarrhoea

Infants, young children, the frail and elderly with acute diarrhoea, may experience fluid and electrolyte depletion. In such cases administration of appropriate fluid and electrolyte replacement (oral rehydration therapy (ORT)) is the most important measure.

If clinical improvement is not observed within 48 hours, the administration of DISCHEM ANTI-DIARRHOEAL TABLETS should be discontinued, and patients should be advised to consult their doctor (see section 4.2).

AIDS Patients

Patients with acquired immunodeficiency syndrome (AIDS) treated with DISCHEM ANTI-DIARRHOEAL TABLETS for diarrhoea should have therapy stopped at the earliest signs of abdominal distension (see section 4.3). There have been reports of toxic megacolon in AIDS patients with infectious colitis from both viral and bacterial pathogens treated with DISCHEM ANTI-DIARRHOEAL TABLETS (see section 4.3).

Abuse and misuse

Abuse and misuse of loperamide, as an opioid substitute, have been described in individuals with opioid addiction (see section 4.9).

Constipation, abdominal distension or subileus

Discontinue use immediately if constipation, abdominal distension or subileus develops (see sections 4.2 and 4.3).

Acute ulcerative colitis or pseudomembranous colitis

Do not use in patients with acute ulcerative colitis or pseudomembranous colitis associated with broad spectrum antibiotics (see section 4.3).

Cardiac events

Cardiac events including QT interval and QRS complex prolongation, torsades de pointes have been reported in association with overdose. Some cases had a fatal outcome (see section 4.9). Patients should not exceed the recommended dose and/or the recommended duration of treatment. Overdose can unmask existing Brugada syndrome.

Medical advice

If no response is obtained within 48 hours medical advice should be sought (see section 4.2).

Paediatric population

Do not administer to children under 6 years (see section 4.3).

4.5. Interaction with other medicines and other forms of interaction

Quinidine or Ritonavir

Non-clinical data have shown that loperamide, as contained in DISCHEM ANTI-DIARRHOEAL TABLETS, is a P-glycoprotein substrate. In two separate studies, 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 with concomitant administration with quinidine, but not with ritonavir; there was evidence of respiratory suppression. The clinical relevance of this pharmacokinetic interaction with P- glycoprotein inhibitors, when loperamide is given at recommended dosages (2 mg, up to 16 mg maximum daily dose), is unknown.

Gemfibrozil and/or Itraconazole

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 CNS effects as measured by psychomotor tests (i.e., subjective drowsiness and the Digit Symbol Substitution Test).

Ketoconazole

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.

Desmopressin

Concomitant treatment with oral desmopressin resulted in a 3-fold increase of desmopressin plasma concentrations, presumably due to slower gastrointestinal motility.

Medicines with similar pharmacological properties and those that accelerate gastrointestinal transit

It is expected that medicines with similar pharmacological properties may potentiate loperamide's, as contained in DISCHEM ANTI-DIARRHOEAL TABLETS, effect and that medicines that accelerate gastrointestinal transit may decrease its effect.

4.6. Fertility, pregnancy and lactation

Pregnancy

The safety of DISCHEM ANTI-DIARRHOEAL TABLETS in pregnancy has not been established (see section 4.3).

Breastfeeding

Loperamide may appear in human breast milk. Therefore, DISCHEM ANTI-DIARRHOEAL TABLETS is not recommended during breastfeeding (see section 4.3).

Women who are pregnant or breast-feeding infants should therefore be advised to consult their doctor for appropriate treatment.

Fertility

The effect on human fertility has not been evaluated.

4.7. Effects on ability to drive and use machines

DISCHEM ANTI-DIARRHOEAL TABLETS has moderate influence on the ability to drive or operate machinery.

Since adverse reactions such as loss of consciousness, depressed level of consciousness, tiredness, dizziness, or drowsiness have been reported in patients taking DISCHEM ANTI-DIARRHOEAL TABLETS, patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that DISCHEM ANTI-DIARRHOEAL TABLETS does not adversely affect their ability to do so (see section 4.8)

4.8. Undesirable effects

a) Summary of the safety profile

The most commonly 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 or chronic diarrhoea and post-marketing experience.

System organ class	Frequent	Less frequent
Immune system disorders		Allergic reactions, hypersensitivity reactions including anaphylactic shock and anaphylactoid reactions
Nervous system disorders	Headache, dizziness	Somnolence, drowsiness, abnormal coordination, depressed level of consciousness, hypertonia, loss of consciousness, stupor
Eye disorders		Miosis
Gastrointestinal disorders	Constipation, dry mouth, flatulence, abdominal cramp, colic, nausea, vomiting, meteorism, abdominal pain	Abdominal discomfort, upper abdominal pain, abdominal distension, dyspepsia, ileus (including reversible paralytic ileus, at high doses), megacolon including toxic megacolon, glossodynia, increased risk of abdominal pain, including pancreatitis
Skin and subcutaneous tissue disorders		Skin rash, urticaria, pruritus, angioedema, and bullous eruptions, including Stevens-Johnson Syndrome, erythema multiforme and toxic epidermal necrolysis

Renal and urinary disorders		Urinary retention
General disorders		Fatigue

c) Description of selected adverse reactions

A number of the adverse events reported during the clinical investigations and post-marketing experience with loperamide, as contained in DISCHEM ANTI DIARRHOEAL TABLETS are also frequent symptoms of the underlying diarrhoeal 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of DISCHEM ANTIDI-ARRHOEAL TABLETS is important. It allows continued monitoring of the benefit/risk balance of DISCHEM ANTI-DIARRHOEAL TABLETS. Healthcare providers are asked to report any suspected adverse reactions to **SAHPRA** via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088

4.9. Overdose

Symptoms

Overdosage may result in constipation.

In case of overdosage (including relative overdose due to hepatic dysfunction), depression of the central nervous system (e.g. stupor, coordination abnormality, somnolence, miosis,

muscular hypertonia and respiratory depression), urinary retention, constipation and paralytic ileus may occur. Excessive inhibition of peristalsis with nausea and dryness of the mouth.
Children and patients with hepatic dysfunction may be more sensitive to central nervous system depressant effects of loperamide than adults.
Convulsions have been reported in children under the age of 2 years.
In individuals who have intentionally ingested overdoses of loperamide HCl, cardiac events such as QT interval and QRS complex prolongation and/or serious ventricular dysrhythmias, including Torsade de Pointes, cardiac arrest and syncope have been observed (see section 4.4). Fatal cases have also been reported.
Abuse, misuse and/or overdose with excessively large doses of loperamide, may unmask Brugada syndrome.

Treatment

Treatment is symptomatic and supportive. In cases of overdose, ECG monitoring for QT interval prolongation should be initiated. If the patient develops respiratory depression, airway obstruction, vomiting with impaired consciousness or other CNS symptoms of overdose. Naloxone can be given as an antidote. Since the duration of action of loperamide, as in DISCHEM ANTI-DIARRHOEAL TABLETS, 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 central nervous system depression.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Category and Class: A 11.9 Medicines acting on gastrointestinal tract:

Antidiarrhoeals.

Pharmacotherapeutic group: Antipropulsives

ATC code: A07 DA03

Mechanism of action

DISCHEM ANTI-DIARRHOEAL TABLETS is a piperidine derivative. Loperamide hydrochloride inhibits hypermotility by direct action on the bowel wall. It slows gastro-intestinal motility by effects on the circular muscles (reflex phase) and longitudinal muscles (preparatory and reflex phases) of the intestine.

Loperamide hydrochloride normalises the stool in both chronic and acute diarrhoea.

5.2. Pharmacokinetic properties

Absorption

DISCHEM ANTI-DIARRHOEAL TABLETS is partially absorbed in the gastro-intestinal tract, 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.

Biotransformation

Loperamide is almost completely extracted by the liver, where it is predominantly metabolised, conjugated and excreted via the bile. Oxidative N-demethylation is the main metabolic pathway for loperamide and is mediated mainly through CYP3A4 and CYP2C8. It undergoes considerable first-pass metabolism in the liver therefore, plasma concentrations of unchanged medicine remain extremely low.

Elimination

The half-life of loperamide is about 11 hours with a range of 9 to 14 hours. Excretion of the unchanged loperamide and the metabolites mainly occurs through the faeces.

Special populations

Paediatrics:

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

Macrogol, magnesium stearate, mannitol, starch (maize), and talc (purified).

6.2. Incompatibilities

Not applicable

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store at or below 25 ºC.

6.5. Nature and contents of container

Polyvinylchloride/aluminium foil blister packs of 6 tablets.

6.6. Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

8. REGISTRATION NUMBER

28/11.9/0140

9. DATE OF FIRST AUTHORISATION

12 March 1996

10. DATE OF REVISION OF TEXT

06 June 2024

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