1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

GASTRON TABLETS 2 mg

GASTRON SYRUP 1 mg/5 ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of GASTRON TABLETS contains 2 mg of loperamide hydrochloride.

Contains sugar: Mannitol 80,0 mg

Each 5 ml of GASTRON SYRUP contains 1 mg of loperamide hydrochloride.

Preservatives:

Methyl parahydroxybenzoate 0,072 % *m/v*

Propyl parahydroxybenzoate 0,008 % *m/v*

Contains sweetener: Saccharin sodium 12,50 mg

Sugar free

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

GASTRON 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.

Syrup.

GASTRON SYRUP is a clear red liquid with a raspberry odour.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

GASTRON is indicated for:

- The control of acute and chronic diarrhoea.
- The control of intestinal transit time in patients with ileostomies, colostomies and other intestinal resections.

GASTRON SYRUP is indicated for: Inhibition of peristalsis and slowing intestinal transit time in children below 6 years of age.

4.2. Posology and method of administration

Posology

Adults

Acute Non-specific Diarrhoea

The usual initial dose of GASTRON TABLETS is two tablets (4 mg) followed by one tablet (2 mg) after each loose stool, up to a total of 8 tablets (16 mg) daily.

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 GASTRON as soon as diarrhoea is under control.

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

Chronic Non-specific Diarrhoea (consult your doctor)

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

The initial dosage is 2 to 4 tablets of GASTRON TABLETS daily in divided doses for adults.

The initial dose should be adjusted until 1 to 2 solid stools per day are obtained.

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, GASTRON should be used with caution in such patients because of reduced first pass metabolism.

Paediatric population

GASTRON TABLETS should not be administered to children under 5 years.

Important: Stop GASTRON SYRUP as soon as diarrhoea is under control.

Acute Non-specific Diarrhoea

In acute diarrhoea, if clinical improvement is not observed within 48 hours, the administration of GASTRON SYRUP should be discontinued and patients should be advised to consult their doctor.

CHILDREN 2 TO 5 YEARS (13 kg to 20 kg body mass)

One medicine measure (5 ml) of GASTRON SYRUP three times a day for the first day, followed by one medicine measure (5 ml) per 10,0 kg body mass after each loose stool. The total daily dose should not exceed 3 medicines measures (15 ml).

CHILDREN 5 TO 8 YEARS (20 kg to 30 kg body mass)

One medicine measure (5 ml) of GASTRON SYRUP four times a day for the first day, followed by one medicine measure (5 ml) per 10,0 kg body mass after each loose stool.

The total daily dose should not exceed 4 medicines measures (20 ml).

CHILDREN 8 TO 12 YEARS (over 30 kg)

Two medicine measures (10 ml) of GASTRON SYRUP three to four times a day, for the first day followed by one medicine measure (5 ml) per 10,0 kg body mass after each loose stool.

The total daily dose should not exceed 8 medicine measures (40 ml).

Chronic non-specific diarrhoea

With individual adjusted dosage it is usually possible to obtain a virtually normal bowel movement. Starting dose is 1 medicine measure (5 ml) per 12, 5 kg body mass a day for children.

The daily dose should be adjusted until 1 to 2 solid stools per day are obtained. This is usually achieved on a maintenance dose of half to 2 medicine measures (2,5 ml to 10 ml) daily.

If constipation occurs, the dosage should be decreased.

Method of administration

For oral administration.

4.3. Contraindications

GASTRON is contraindicated in:

- Patients with hypersensitivity to loperamide hydrochloride or to any excipients in GASTRON (see section 6.1).
- Infants below 24 months of age.

- Primary therapy in patients with acute dysentery, which is characterised by blood in stools and high fever.
- 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.
- Where constipation is present or in patients with inflammatory bowel disease.
- The treatment of acute infective diarrhoea.
- Hepatic dysfunction, as it may result in relative overdosing.
- Safety in pregnancy has not been established.
- GASTRON TABLETS should not be administered to children under 5 years.

In general, GASTRON should not be used when inhibition of peristalsis must be avoided due to the possible risk of significant sequelae including ileus, megacolon and toxic megacolon.

4.4. Special warnings and precautions for use

Treatment of diarrhoea with GASTRON is only symptomatic. Whenever an underlying aetiology can be determined, specific treatment should be given when appropriate (or when indicated).

Acute diarrhoea

In patients with diarrhoea, especially in infants, fluid and electrolyte depletion may occur. In such cases administration of appropriate fluid and electrolyte replacement (oral rehydration therapy (ORT)) is the most important measure.

Medical advice

Patients should be told not to continue medication if no response is obtained within 48 hours; medical advice should then be sought (see section 4.2).

Constipation, abdominal distension or subileus

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

AIDS Patients

Patients with acquired immunodeficiency syndrome (AIDS) treated with loperamide, as contained in GASTRON, for diarrhoea should have therapy stopped at the earliest signs of abdominal distension. There have been reports of toxic megacolon in AIDS patients with infectious colitis from both viral and bacterial pathogens treated with loperamide, as in GASTRON.

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 and torsades 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.

Abuse and misuse

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

Excipients

GASTRON SYRUP contains parahydroxybenzoates which may cause allergic reactions (possibly delayed).

4.5. Interaction with other medicines and other forms of interaction

Quinidine or Ritonavir

Non-clinical data have shown that loperamide, as in GASTRON, 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, as in GASTRON (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 effect and that medicines that accelerate gastrointestinal transit may decrease its effect.

4.6. Fertility, pregnancy and lactation

Pregnancy

The safety of GASTRON in pregnancy has not been established (see section 4.3).

Breastfeeding

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

Fertility

There are no data available.

4.7. Effects on ability to drive and use machines

GASTRON 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, and drowsiness have been reported in patients receiving GASTRON, patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that GASTRON 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

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 in GASTRON 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.

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. 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/ +27 (0)11 239-6200

4.9. Overdose

Symptoms

Overdosage may result in constipation.

Depression of the central nervous system may be seen in overdosage.

Excessive inhibition of peristalsis with nausea and dryness of the mouth.

In case of overdose (including relative overdose due to hepatic dysfunction), central nervous system depression (e.g. stupor, coordination abnormality, somnolence, miosis, muscular hypertonia and respiratory depression), urinary retention, constipation and paralytic ileus may occur.

Children 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, QT interval and QRS complex prolongation and/or serious ventricular dysrhythmias, including Torsade de Pointes, 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. Naloxone can be given as an antidote. Since the duration of action of GASTRON 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: A07DA03

Mechanism of action

Loperamide is a piperidine derivative. Loperamide hydrochloride inhibits hypermotility by direct action on the bowel wall. It slows gastrointestinal motility by effects on the circular (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

Loperamide is partially absorbed in the gastrointestinal tract. It undergoes considerable first-pass metabolism in the liver, 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. Due to this very high first pass effect, 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. Unchanged loperamide and its metabolites is excreted mainly in 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

GASTRON TABLETS:

Magnesium stearate, mannitol, polyethylene glycol, starch maize, purified talc.

Contains sugar: Mannitol 80,0 mg

GASTRON SYRUP:

Colour Ponceau 4R red (C.I.16255), flavour raspberry, glycerol, methyl parahydroxybenzoate, propyl parahydroxybenzoate, purified water, saccharin sodium, sodium hydroxide pellets (for pH adjustment).

Preservatives:

Methyl parahydroxybenzoate 0,072 % *m/v*

Propyl parahydroxybenzoate 0,008 % *m/v*

Contains sweetener: Saccharin sodium 12,50 mg

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

GASTRON Tablets: 36 months

GASTRON Syrup: 24 months

6.4. Special precautions for storage

Store at or below 25 °C.

Keep in original packaging until required for use.

6.5. Nature and contents of container

GASTRON TABLETS:

6 or 300 tablets are packed in a clear polyvinylchloride blister strip sealed with an aluminium foil backing. The blister strips are packed into an outer cardboard carton together with a leaflet.

Not all packs or pack sizes may be marketed.

GASTRON SYRUP:

50 ml is packed into an amber polyvinylchloride bottle with a white, low density polyethylene snap cap.

50 ml is packed into an amber glass bottle with a black screw-cap, with an expanded polyethylene liner.

Not all packs or pack sizes may be marketed.

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 NUMBERS

GASTRON TABLETS: V/11.9/213

GASTRON SYRUP: V/11.9/214

9. DATE OF FIRST AUTHORISATION

GASTRON TABLETS: 15 November 1988

GASTRON SYRUP: 30 June 1989

10. DATE OF REVISION OF TEXT

16 February 2024

Die Afrikaanse Professionele Inligting is op versoek beskikbaar.

Medias Bristly: 0800 118 088

Namibia: NS1
GASTRON TABLETS: 04/11.9/0018
GASTRON SYRUP: 04/11.9/0017

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