SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DIARZIL 2 mg/125 mg tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains loperamide hydrochloride 2 mg and simeticone 125 mg.
See section 6.1 for a full list of excipients.

3. PHARMACEUTICAL FORM

Tablet.
Greyish white caplets with a score line.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DIARZIL is indicated for the symptomatic treatment of acute diarrhoea in adults and adolescents over 12 years when acute diarrhoea is associated with gas-related abdominal discomfort including bloating, cramping or flatulence.

4.2 Posology and method of administration

The tablets should be taken with liquid.

Adult over 18 years:
Take two caplets initially, followed by one caplet after every loose stool. Not more than 4 caplets should be taken in a day, limited to no more than 2 days.

Adolescents between 12 and 18 years:
Take one caplet initially, followed by one caplet after every loose stool. Not more than 4 caplets should be taken in a day, limited to no more than 2 days.

Use in children:
DIARZIL must not be used in children under 12 years (see section 4.3).

Use in elderly:
No dosage adjustments are required for elderly.

Use in renal impairment:
No dosage adjustments are required in case of renal impairment.

Hepatic impairment:
Although no pharmacokinetic data are available in patients with hepatic insufficiency, DIARZIL should be used with caution in such patients because of reduced first pass metabolism (see section 4.4).

Method of administration
Swallow the correct amount of tablets, fully, with a glass of water.

4.3 Contraindications

- Children less than 12 years of age.
- Hypersensitivity to loperamide hydrochloride, simeticone or any of the excipients listed in section 6.1.
- Patients with acute dysentry, which is characterized by blood in stool and hygh fever.

- Patients with acute ulcerative colitis.
- Patients with pseudomembraneous colitis associated with broad spectrum antibiotics.
- Patients with bacterial enterocolitis caused by invasive organisms including *Salmonella*, *Shigella* and *Campylobacter*.

DIARZIL should not be used when inhibition of peristalsis is to be avoided due to the possible risk of significant sequelea including ileus, megacolon and toxic megacolon. It must be stopped promptly if constipation, ileus or abdominal distension develop.

4.4 Special warnings and precautions for use

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

In patients with (severe) diarrhoea, fluid and electrolyte depletion may occur. It is important than attention is paid to appropriate fluid and electrolyte replacement.

If clinical improvment is not observed within 48 hours, the administration of DIARZIL must be discontinued. Patients should be advised to consult their physician.

Patients with AIDS treated with DIARZIL for diarrhoea 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 hydrochloride.

Although no pharmacokinetic data are available in patients with hepatic impairment, DIARIL should be used with caution in such patients because of reduced first pass metabolism. This medicine must be used with caution in patients with hepatic impairment as it may result in a relative overdose leading to central nervous system (CNS) toxicity. DIARZIL should be used under medical supervision in patients with severe hepatic dysfunction.

Cardiac effects including a QT prolongation and torsades de pointes have been reported in the event of an overdose. In certain cases, the evolution has been fatal (see section 4.9). Patients should not exceed the recommended dose/treatment duration.

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 singl dose) with quinidine, or tironavir, which are both P-glycoprotein inhibitors, resulted in a 2 to 3-fold increase in loperamide plasma concentrations. 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 itraconazol, an inhibitor of CYP3A4 and P-glycoprotein, resulted in 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 increased loperamide by approximately 4-fold increase in peak plasma levels of loperamide and a 13-fold increase in total plasma exposure. These increases were not associated with measured CNS effects, as measured by psychomotor tests (i.e. subjective drowsiness and DSST - *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 increased pharmacodynamid 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 effects and that drugs that accelerate gastrointestinal transit may decrease its effect.

Since simeticone is not absorbed from the gastrointestinal tract, no relevant interactions between simeticone and other drugs are expected.

Paediatric population
Interaction studies have been carried out only in adults.

4.6 Fertility, pregnancy and lactation

Use in pregnancy
Safety in human pregnacy has not been established, although form animal studies there are no indications that loperamide or simeticone processes teratogenic or embryotoxic properties. DIARZIL should not be given during pregnacy, especially during the first trimester, unless clinically justified.

Use in lactation
Small amounts of loperamide may appear in human breast milk. Therefore DIARZIL is not recommended during breast-feeding.

Fertility
The effect on human fertility has not be assessed.

4.7 Effects on ability to drive and use machines

DIARZIL has no or only neglictable effect on the ability to drive and use machines. However, tiredness, dizziness, drowsiness may happen in the event of diarrhoea syndromes treated by loperamide hydrochloride (see section 4.8). Consequently, it is advised to be careful in case of driving or using machines.

4.8 Undesirable effects

The safety of loperamide-simeticone was evaluated in 2040 patients who participated in five clinical trials. All patients included in those trials had acute diarrhoea with gas related discomfort and treated with a chewable tablet of loperamide-simeticone. Four trials compared the combination of loperamide and simeticone to loperamide, to simeticone and to a placebo and one trial compared two formulations of loperamide-simeticone to placebo.

The most commonly reported (i.e., ≥ 1 % incidence) ADRs in clinical trials were (with % incidence): dysgeusia (2.6 %) and nausea (1.6 %).

The safety of loperamide HCl was evaluated 2755 patients aged ≥ 12 years who participated in 26 controlled and uncontrolled clinical trials of loperamide HCl used for the treatment of acute diarrhoea. The most common ADRs (> 1 %) reported in these clinical trials were constipation (2.7 %), flatulence (1.7 %), headaches (1.2 %) and nausea (1.2 %).

The safety of loperamide HCl was also evaluated in 321 patients who participated in 5 controlled and uncontrolled clinical trials of loperamide HCl used for the treatment of chronic diarrhoea. The most common ADRs (> 1 %) reported in these clinical trials were flatulence (2.8 %), constipation (2.2 %), dizziness (1.2 %) and nausea (1.2 %).

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 trials of loperamide HCl used for the treatment of acute diarrhoea. The only ADR reported for ≥ 1 % of loperamide HCl-treated patients was vomiting.

Table 1 displays ADRs that have been reported with the use of loperamide-simeticone from either clinical trial of post-marketing experience. Additional ADRs reported with the use of loperamide HCl (one of the components of loperamide-simeticone) are also shown.

The frequency categories are based on clinical trial data with loperamide-simeticone and loperamide HCl and 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 1: Undesirable effect associated to the medicine

System class organ	**Adverse events**		
	Frequency		
	Common	**Uncommon**	**Rare**
Immune system disorders			Hypersensitivity reaction[a], anaphylactic reaction (including anaphylactic shock)[a], anaphylactoid reaction
Nervous system disorders	Headache[b], dysgeusia	Somnolence[a], Dizziness[c]	Loss of consciousness[a], depressed level of consciousness[a], stupor[a], hypertonia[a], coordination abnormality[a]
Eye disorders			Miosis[a]
Gastrointestinal disorders	Nausea	Abdominal pain, abdominal discomfort[b], abdominal pain upper[b], vomiting, constipation, abdominal distension[c], dyspepsia[c], flatulence, dry mouth	Ileus[a] (including paralytic ileus), megacolon[a] (including toxic megacolon[d])
Skin and subcutaneous tissue disorders		Rash	Bulbous eruption (including Stevens-Johnson syndrome[a], toxic epidermal necrolysis[a] and erythema multiform[a]), angioedema[a], urticaria[a], pruritus[a]
Renal and urinary disorders			Urinary retention[a]
General disorders and administration site conditions		Asthenia	Fatigue[a]

[a] 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 combined, including trials in children ≤ 12 years (N = 3683).
[b] Inclusion of this term is based on ADRs reported with loperamide HCl. Frequency category assigned based on clinical trials with loperamide HCl in acute diarrhoea (N = 2755).
[c] Inclusion of this term is based on post-marketing experience with loperamide-simeticone. Frequency category assigned based on clinical trials with loperamide-simeticone in acute diarrhoea (N = 618). Dizziness and abdominal distension were also identified as clinical ADRs with loperamide HCl.
[d] See section 4.4 Special Warnings and Special Precautions for use.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

Symptoms
In case of overdosage (including relative overdosage due to hepatic dysfunction), central nervous system depression (stupor, cp-ordination abnormality, somnolence, miosis, muscular hypertonia, repiratory depression), dry mouth, abdominal discomfort, nausea and vomiting, constipation, urinary retention and paralytic ileus may occur.

Cardiac effects, as QT prolongtion, torsades de pointes, other severe ventricular arythmias, cardiac arrest and syncope have been observed in people who ingested exceessive doses of loperamide hydrochloride (see section 4.4). Fatal outcomes cases have also been reported.

Treatment
If symptoms of overdosage 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 may be indicated. Therefore, the patient should be monitored closely for at least 48 hours in order to detect CNS depression.

Paediatric population
Children may be more sensitive to CNS effects than adults.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antipropulsive antidiarrheals, ATC code: A07DA53

Loperamide hydrochloride
Loperamide binds to the opiate receptor in the gut wall, reducing propulsive peristalsis intestinal transit time and enhancing resorption of water and electrolytes. Loperamide does not change the physiological flora. Loperamide increases the tone of the anal sphincter. DIARZIL does not act centrally.

Simeticone
Simeticone is an inert surface-active agent with antifoaming properties thereby potentially relieving gas-related symptoms associated with diarrhoea.

Simeticone is liquid dimeticone activated with silicon dioxide finely divided to improve the antifoaming activity of silicon.

5.2 Pharmacokinetic properties

Absorption: most ingested loperamide is absorbed from the gut, but as a result of significant first pass metabolism, systemic bioavailability is only approximately 0.3 %. The simeticone component of loperamide-simeticone is not absorbed.

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.

Metabolism: 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 drug remain extremely low.

Elimination: the half-life of loperamide in man is about 11 hours with a range of 9-14 hours. Excretion of the unchanged loperamide and the metabolites occurs through the faeces.

5.3 Preclinical safety data

Acute and chronic studies on loperamide showed no specific toxicity. Results of *in vivo* and *in vitro* studies carried out indicated that loperamide is not genotoxic. In reproduction studies, very high doses (40 mg/kg/day – 20 times the maximum human use level in terms of body surface) loperamide impaired fertility and foetal survival with maternal toxicity in rats. Lower doses had no effects on maternal or foetal health and did not affect peri- and post-natal development.

Non-clinical *in vitro* and *in vivo* trials with loperamide hydrochloride do not indicate any significant effect on cardiac electrophysiology at concentrations corresponding to the therapeutic window (up to 47 times). However, at extremely high concentrations, related to an overdose (see section 4.4), loperamide actcs on cardiac electrophysiology, by the inhibition of potassium channels (hERG) and sodium channels, and provoque arythmias.

Simeticone is a member of the class of linear polydimethylsilicones, which have been in wide general and medicinal use for many years and are regarded as biologically inert and not exhibiting toxic properties and has not been the subject of specific animal toxicity studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tribasic calcium phosphate, microcristalline cellulose, croscarmellose sodium, colloidal anhydrous silica, magnesium stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original container, below 30 °C.

6.5 Nature and contents of container

Tablets are packed in a PVC-PVdC/aluminium blister of 12 tablets, in a cardboard box.

6.6 Special precautions for disposal

No special requirements.

7. CATEGORY OF DISTRIBUTION

☒ Over-the counter medicine ☐ Prescription only medicines

List II

8. MARKETING AUTHORISATION HOLDER

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10. DATE OF REVISION OF THE TEXT

01/2019