# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

FLATORIL® Hard capsules

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Per capsule:
Clebopride (INN) (acid malate), 0.5 mg
Simethicone, 200 mg

For list of excipients, see 6.1.

## 3. PHARMACEUTICAL FORM

Hard capsules.

## 4. CLINICAL PARTICULARS

### 4.1. Therapeutic indications

FLATORIL is indicated in:
- Symptomatic treatment of functional gastrointestinal motility disorders associated with flatulence in adults.
- Preventive treatment of flatulence in radiologic explorations of the digestive tract in adults.
- Symptomatic treatment of post-operative nausea and vomiting associated with flatulence in adults.

### 4.2. Posology and method of administration

- Adults:

For symptomatic treatment of functional gastrointestinal motility disorders that occur with flatulence, and for symptomatic treatment of postoperative nausea and vomiting that occur with flatulence: 1 capsule 3 times a day, before each meal. It may be advisable to reduce in the dose in some cases.

For the prevention of excess gas in radiological examinations of the gastrointestinal tract: 1 capsule 2 hours before the test.

### 4.3. Contraindications

- Do not administer in case of hypersensitivity to clebopride, simethicone or any of the ingredients in this pharmaceutical product.
- Do not administer to patients for whom stimulation of gastrointestinal motility could be harmful (gastrointestinal haemorrhage, obstruction or perforation).
- Do not administer to patients with confirmed neuroleptic-induced tardive dyskinesia.
- Do not administer to patients with epilepsy, Parkinson's disease or other extrapyramidal disorders.

### 4.4. Special warnings and precautions for use

Doses higher than those recommended may increase the possibility of extrapyramidal reactions, especially in elderly patients.

Clebopride should be used with caution in patients with severe hepatic or renal failure, as the plasma concentrations of the drug can be increased or prolonged, increasing its effect.

Attention should be paid to any increase in prolactin levels, especially in patients with breast cancer or prolactin-secreting pituitary adenoma..

## 4.5. Interaction with other medicinal products and other forms of interaction

In general, due to its mechanism of action (increased gastrointestinal motility), clebopride can alter the pharmacokinetics of any other concomitantly administered medicine.

It can specifically cause the following interactions:

- Clebopride can enhance the effects of phenothiazines and other antidopaminergic agents on the central nervous system.

- Clebopride can reduce the effects of digoxin and cimetidine.

- Anticholinergic agents and narcotic analgesics can neutralise the effect of clebopride in the gastrointestinal tract.

- Clebopride can enhance the sedative effects of alcohol, anxiolytics, hypnotic agents or narcotics.

- The concomitant administration of IMAO may increase the risk of adverse reactions.

Simethicone does not present drug interactions, as it is an extremely inert, and therefore pharmacologically inactive.

## 4.6. Pregnancy and lactation

**Pregnancy**
Data on the use of clebopride in pregnant women are limited and there are no studies for simethicone. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of clebopride during pregnancy, especially during the first three months of pregnancy.

**Lactation**
It is not known whether the active substances are excreted in mother's milk and whether this could affect newborns. As a precautionary measure, it is preferable to avoid the use of clebopride during lactation.

**Fertility**
There are no fertility data with clebopride in humans.

## 4.7. Effects on the ability to drive and use machines

In the course of treatment, should avoid situations requiring high state fo alertness, such as driving or the use of dangerous machines.

## 4.8. Undesirable effects

During all the clinical trials, and based on post-marketing experience, the following adverse reactions were reported. They are grouped below by organ system and estimated frequency: very common (≥1/10), common (≥1/100 a < 1/10), uncommon (≥1/1.000 a < 1/100), rare (≥1/10.000 to < 1/1.000), very rare and isolated cases (< 1/10.000).

**Nervous system disorders**
*Rare:* Extrapyramidal disorders, dystonia (1), dyskinesia, tardive dyskinesia (2), sedation, tremor and somnolence.

**Endocrine disorders**
*Very rare*: Hyperprolactinaemia

**Reproductive system and breast disorders**
*Very rare:* galactorrhoea, gynaecomastia, erectile dysfunction and amenorrhea.

(1) The most commonly reported cases of dystonia affected the neck, face and tongue.
(2) Tardive dyskinesia was reported in elderly patients during long-term treatments.
(3) Hyperprolactinaemia, galactorrhoea, amenorrhea, gynaecomastia and erectile dysfunction were reported in long-term treatments.

### 4.9. Overdose

Overdosage may cause somnolence, disorientation and extrapyramidal disorders; they normally disappear when the treatment is suspended.

A stomach lavage and symptomatic medication should be administered if symptoms persist. Extrapyramidal disorders are controlled with the administration of antiparkinsonian medication, anticholinergic agents or antihistaminic agents with anticholinergic properties.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1. Pharmacodynamic properties

ATC classification: A03FA – Propulsive agents

**Clebopride**
Substituted benzamides are a pharmacological group, also known as orthopramides that specifically block selective groups of dopaminergic receptors in the central nervous system (CNS). Basically, these drugs are not only applied to the CNS but also to the digestive system, either as antiemetics or as gastrointestinal peristalsis regulators. The group of substituted benzamides includes the following substances: clebopride, metoclopramide, domperidone, bromopride, alizapride, sulpiride, thiapride and remoxipride.

Clebopride is an orthopramide which, through pharmacological and clinical research, has been shown to regulate gastrointestinal motility. It is also an effective antiemetic and prokinetic, and a blocking agent for digestive disorders caused by stress.

It has antidopaminergic properties and a series of pharmacological properties that show, on the one hand, selectivity for dopaminergic receptors over other types of receptors, and on the other, selectivity for dopamine among different receptor populations. Clebopride was particularly active in antiemetic trials on the fourth ventricle chemoreceptor trigger zone, in trials for central activity on the mesolimbic system related to tranquillising activity, and on a gastrointestinal level for peristalsis regulation and gastric emptying.

On a central level, it is a dopamine D2 receptor blocker in the chemoreceptor trigger zone, interfering with the integration of afferent emetogenic impulses. On a peripheral level, D2 receptor blockage increases intestinal peristalsis (prokinetic effect), which is enhanced due to its action as an indirect cholinergic agent, facilitating acetylcholine release by intestinal postganglionic neurones.

**Simethicone**
Simethicone, with a direct local effect, supplements the effect of clebopride, absorbing gas molecules in the gastrointestinal tract. Physiologically, simethicone is extremely inert and therefore not pharmacologically active. It changes the superficial tension of gas bubbles, causing them to unite.

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The association of clebopride and simethicone reduces gastric distension and improves the quality of ultrasound images of the organs located behind the stomach, such as the gall bladder, different portions of the pancreas and the left kidney. The administration of such drugs improves these images and increases the rate of gastric emptying and gastrointestinal transit, reducing gas bubble formation and retention.

The results of experimental studies in animals and clinical trials in humans have shown that clebopride is a dopamine receptor blocking agent, thus increasing lower oesophageal sphincter pressure and gastric emptying. The effect of simethicone as an anti-foaming agent supplements the effect of clebopride, justifying their association.

### 5.2. Pharmacokinetic properties

**Clebopride**
Pharmacokinetic studies cannot be conducted in humans because of the large volume of distribution of

clebopride and considering the low doses administered. Therefore, the pharmacokinetic data are based on animal experimentation studies.

Orally, clebopride is rapidly absorbed, obtaining peak plasma concentrations of 2.19 µg/ml (oral doses of 0.5 mg) after 1-2 h. It is metabolised in the liver, producing N-desbenzylclebopride. Unmetabolised clebopride is rapidly eliminated, while the metabolite has a long elimination half life.

The absorption, distribution and elimination of clebopride have been studied in animals after its intravenous and oral administration, finding good distribution of the drug. However, the data obtained in the animal experimentation studies suggest that clebopride has a greater volume of distribution in humans.

The hepatic metabolism of clebopride was studied by incubating the drug with the microsomal fraction of animal liver, and global metabolism was studied by analysing urine samples after oral administration. It can be said that the global metabolic biotransformation processes observed in *in vitro* and *in vivo* experiments highlight the importance of the following stages of clebopride metabolism: a) N-debenzylation, through an intermediate step of oxidation of the methylene carbon; b) oxidation of the piperidine ring on both nitrogen and adjacent carbon; c) rupture of the amide link, and d) conjugation of the aromatic amine group with glucuronic acid.

**Simethicone**
Simethicone is a dimethylpolysiloxane that reduces the surface tension when air bubbles join or when they break. It has no systemic effects, as it is not absorbed. Simethicone alone has been used both to treat tympanites and to improve the quality of ultrasound and endoscopic images.

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Pharmacokinetic studies have shown good clebopride absorption in the presence of simethicone, a drug that is not absorbed and is pharmacologically inert.

### 5.3. Preclinical safety data

In both clinical trials and post-marketing experience, FLATORIL presents a good safety profile with regards to incidence of adverse reactions, thus confirming the good tolerance shown in a wide range of preclinical toxicology studies.

As FLATORIL is innocuous, the LD $DL_{50}$ in rats or mice could not be determined after administration of the maximum quantity to be ingested by these animals, 10 g/kg (capsules).

The administration of high doses in chronic toxicity studies in both rats and dogs caused effects related to exaggerated pharmacological response to dopamine receptor-blocking agents.

Teratogenicity studies with clebopride in rats and rabbits showed no teratogenic potential.

According to the Ames test, clebopride showed no mutagenic potential in the studied strains.

After administration of doses of 2.5 and 5 g/kg of FLATORIL in rats, for 21 days, good gastrointestinal tract tolerance was observed.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1. List of excipients

Povidone, sodium laurylsulphate, colloidal silica and croscarmellose sodium. Capsule components: titanium dioxide (E -171), erythrosine (E-127), indigotine (E- 132) and gelatine.

### 6.2. Incompatibilities

None described.

### 6.3. Shelf life

36 months.

### 6.4. Special precautions for storage

Store below 30ºC.

### 6.5. Nature and contents of container

PVC/aluminium blister. Box with 45 capsules.

## 7. MARKETING AUTHORISATION HOLDER

ALMIRALL, S.A.
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## 8. DATE OF REVISION OF THE TEXT

Mod. S.P.C. 01. 0 (07/12/16)