1. NAME OF THE MEDICINAL PRODUCT

Cidine 1 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1 mg of cinitapride (acid tartrate).
Excipient with known effect: 111 mg of lactose.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Pale Yellow, bi-flat circular tablets scored on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of mild-to-moderate dysmotility-type dyspepsia.
- As coadjuvant treatment for gastro-oesophageal reflux in patients in whom proton pump inhibitors have proved insufficient.

4.2 Posology and method of administration

Adults (over 20 years of age): 1 tablet 3 times a day, 15 minutes before each meal.

It is not more effective and is not advisable to increase the recommended dose.

Paediatric population:
It is not advisable to administer cinitapride to children and adolescents due to lack of experience regarding its use in these age groups.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Cinitapride must not be administered to patients in whom gastric motility stimulation could be harmful due to the presence of haemorrhages, obstructions or perforations or to patients with proven neuroleptic-induced tardive dyskinesia.

4.4 Special warnings and precautions for use

Tardive dyskinesia may occur in elderly patients receiving long-term treatment.
Although in vitro studies at much higher plasma concentrations than those found in clinical practice suggest that cinitapride may prolong cardiac repolarisation, in vivo studies in both animals and humans have shown no effect on the electrocardiogram and particularly on the QT interval.

Warnings about excipients
This medicinal product contains lactose. Patients with hereditary galactose intolerance, Lapp lactase deficiency (deficiency observed in some parts of Lapland) or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

The stimulation of gastric emptying caused by cinitapride may alter the absorption of certain drugs. Patients must tell their doctor if they are being treated with other drugs. It enhances the effects of phenothiazines and other dopamine antagonists on the Central Nervous System.

It may decrease the effect of digoxin by reducing its absorption.
Its actions on the gastrointestinal tract may be reduced by atropinic anticholinergics and opioid analgesics.

If administered together with alcohol, tranquillisers, hypnotics or narcotics, it enhances the sedative effects.

In vitro, cinitapride is metabolised primarily by CYP3A4 (and, to a lesser degree, by CYP2C8), so the concomitant use of oral or parenteral drugs that significantly inhibit this isoenzyme could alter its pharmacokinetics. Examples of such drugs are:

- azole antifungals such as ketoconazole, itraconazole, miconazole and fluconazole. In any case, a study in humans at repeated doses of cinitapride in the absence and presence of ketoconazole has shown that there is little pharmacokinetic interaction, as the average values of the area under the cinitapride curve increased approximately twofold (range: 0.9-4.3; 95% CI: 1.5-2.4).
- HIV protease inhibitors, primarily indinavir and ritonavir.
- Macrolide antibiotics such as erythromycin, clarithromycin or troleandomycin.
- The antidepressant nefazodone.

4.6 Fertility, pregnancy and lactation

Fertility
There are no fertility data regarding the use of cinitapride in humans.

Pregnancy
There are no data regarding the use of cinitapride in pregnant women. Studies in animals do not suggest any direct or indirect harmful effects in terms of reproductive toxicity. As a precautionary measure, cinitapride should not be used during pregnancy.

If its use is necessary, the doctor must assess the risk/benefit ratio.

Lactation
It is not known whether cinitapride is excreted in human milk. As a precautionary measure, cinitapride should not be used during lactation.

4.7 Effects on ability to drive and use machines

Situations requiring particular alertness, such as driving vehicles or handling dangerous machinery, must be avoided during treatment with cinitapride.

4.8 Undesirable effects

Cinitapride has been widely studied in healthy adult volunteers and in patients with gastrointestinal motility disorders, both in placebo-controlled trials and in other comparative and non-comparative open-label clinical trials. There is also post-marketing experience since cinitapride was first authorised in 1989.

Although the clinical pharmacology of cinitapride has not shown drowsiness or alterations in psychometric testing in subjects who took the recommended doses, some patients may notice mild sedation or drowsiness.

The following table lists the undesirable effects that have been reported in clinical trials and in post-marketing experience, which are classified as follows: 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).

Nervous system disorders	Uncommon: drowsiness Not known*: extrapyramidal reactions**
Skin and subcutaneous tissue disorders	Not known*: rash, pruritus, angioedema
Reproductive system and breast disorders	Not known*: gynecomastia, galactorrhoea

*Frequency not known (cannot be estimated from the available data)

**Extrapyramidal reactions may occur, with muscle spasms in the face, neck and tongue, which disappear when treatment is discontinued

4.9 Overdose

Overdose can result in drowsiness, disorientation and extrapyramidal reactions that normally disappear when treatment is discontinued. Should the symptoms persist, gastric lavage should be performed and symptomatic medication administered. Extrapyramidal reactions are controlled by administering antiparkinson drugs, anticholinergics or antihistamines with anticholinergic properties.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Prokinetics; ATC code: A03FA

Cinitapride is an orthopramide with prokinetic activity in the gastrointestinal tract that has a pronounced procholinergic action. By blocking presynaptic serotonin receptors, it increases the release of serotonin, resulting in greater serotoninergic activity. Its antidopaminergic activity, although mild, contributes to the therapeutic effect.

The administration of cinitapride in laboratory animals has shown that its prokinetic action is effective from the oesophageal sphincter to the large intestine. Cinitapride favours gastric emptying of semi-solids in rats; it stimulates motility in isolated guinea pig ileum; it increases intraluminal pressure in the stomach, duodenum and ileum of conscious dogs; and it increases lower oesophageal sphincter pressure and mechanical activity of the duodenum and colon in anaesthetised dogs. It accelerates intestinal transit in mice.

In clinical trials conducted in patients and in healthy volunteers, cinitapride has been shown to antagonise gastroparesis and levodopa-induced vomiting.
In a placebo-controlled study, cinitapride significantly accelerated the gastric emptying time in patients with a pathological delay in gastric emptying. Cinitapride improves the symptoms of patients with dyspepsia associated with delayed gastric emptying and gastrointestinal transit.

In patients with gastro-oesophageal reflux, cinitapride reduces the number and duration of reflux episodes, as well as the time that the oesophageal pH is less than 4, therefore considerably improving the symptoms of this disease. Its efficacy in this case may be due not only to the increase in oesophageal sphincter pressure, but also to the fact that it aids gastric emptying.

5.2 Pharmacokinetic properties

As regards the pharmacokinetics of cinitapride in rats following intravenous administration, the best fit was obtained with a bicompartmental model, with a large volume of distribution (9.9 l/kg) and a relatively slow elimination rate (51-83 min). No metabolites were detected in plasma with this route of administration.

It was shown that it undergoes significant first-pass metabolism when administered orally. A total of 30% of the administered dose was recovered in the bile after 48 hours.

Studies carried out in vitro in recombinant microsomes suggest that cinitapride is metabolised by

CYP3A4 and, to a lesser degree, by CYP2C8.

The pharmacokinetic studies conducted in humans have been carried out after oral and intramuscular administration with doses higher than the therapeutic dose, due to the lack of a sufficiently sensitive analytical method to detect plasma concentrations that reach the recommended dose.

These studies have shown that after oral administration of cinitapride, maximum plasma levels are reached after two hours. The elimination half-life is 3 to 5 hours during the first 8 hours, with a residual half-life of more than 15 hours after that, although with extremely low plasma levels.

On the basis of this pharmacokinetic profile, the most suitable dose regimen is to distribute its administration in three doses per day. No accumulation has been observed after repeated administration of cinitapride.

5.3 Preclinical safety data

Cinitapride has a low toxicity and a high therapeutic index. Subchronic and chronic toxicity studies in both rats and dogs have not resulted in unexpected effects, confirming the long-term safety of cinitapride.

Reproductive toxicity and mutagenicity studies have not revealed any abnormalities. Electrophysiological studies in vitro show that, under certain conditions, cinitapride can prolong cardiac repolarisation. At concentrations of more than 100 times the plasma concentration found in humans at the therapeutic dose, cinitapride dose-dependently blocks HERG channels expressed in HEK 293 cells and prolongs action potential duration in isolated pig Purkinje fibres. However, at very high doses (30 mg/kg orally) it has no effect on the QT interval in electrophysiological studies in vivo in conscious guinea pigs.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium starch glycolate (potato starch).
Cellulose powdered.
Lactose anhydrous.
Silica colloidal anhydrous.
Magnesium stearate (E470b).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.
Keep in its pack, away from excessive heat and moisture.

6.5 Nature and contents of container

PVC/Aluminium blister. Pack containing 50 tablets.

6.6 Special precautions for disposal

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

ALMIRALL, S.A.
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08022 – Barcelona

8. DATE OF REVISION OF THE TEXT

Mod. F.T.6.0 (21/05/12)