DRAFT LEAFLET
HIDRASEC
Racecadotril

1. NAME OF THE MEDICINAL PRODUCT

Hidrasec, 100 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 100 mg of racecadotril.

Excipients with known effect:
Each capsule contains 41 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

Ivory colored capsules

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

HIDRASEC is indicated for adjunct treatment for adult diarrhea patient when oral rehydration therapy is not sufficient.

4.2 Posology and method of administration

Hidrasec should be given in conjunction with oral or parenteral rehydration therapy in patients where dehydration has occurred or is suspected.

Age 15 years and above

Treatment should be initiated with a single 100 mg capsule given regardless of the time. Further treatment is given approximately 8 hourly until cessation of diarrhea.

The daily dose should not exceed 400 mg. If symptoms persist for more than 7 days then the patient should seek medical advice.

Elderly Subjects

An adjustment of dose is not necessary in elderly subjects.

Ages under 15 years

HIDRASEC capsules are not recommended for use in children under 15 years.

If the diarrhea persist for more than 3 days and in the case of severe diarrhea, the presence of blood in the stool, fever or vomiting, further observation and evaluation is necessary.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Patients who have reported angioedema with angiotensin converting enzyme inhibitors (such as captopril, enalapril, lisinopril, perindopril, ramipril) should not take racecadotril.

HIDRASEC capsules should not be used in children.

4.4 Special warnings and precautions for use

Precautions for use
The administration of Hidrasec does not modify the usual rehydration regimens.

The presence of bloody or purulent stools and fever may indicate the presence of invasive bacteria as a reason for diarrhoea or the presence of other severe disease, warranting causal (e.g. antibiotic) treatment or further investigation. Therefore, racecadotril should not be administered under these conditions. Racecadotril may be given concomitantly with antibiotics in case of acute diarrhoea with a bacterial cause as a complementary treatment.
Use of racecadotril in antibiotic-associated diarrhoea and chronic diarrhoea is not recommended due to insufficient data.

There are limited data in patients with renal or hepatic impairment. These patients should be treated with caution (see section 5.2).

There is a possible reduced availability in patients with prolonged vomiting.

Warning:
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Occurrence of skin reactions has been reported with the use of the product. These are in most cases mild and do not require treatment but in some cases they can be severe, even life-threatening.
Association with racecadotril cannot be fully excluded. When experiencing severe skin reactions, the treatment has to be stopped immediately.

Hypersensitivity/Angioedema have been reported in patients with racecadotril. This may occur at any time during therapy. Patients with a history of angioedema unrelated to racecadotril therapy may be at increased risk of angioedema.

4.5 Interaction with other medicinal products and other forms of interaction

Angiotensin converting enzyme inhibitors (such as captopril, enalapril, lisinopril, fosinopril, perindopril, ramipril) are known to induce angioedema. This risk could be increased in presence of racecadotril.

In humans, the concomitant treatment with racecadotril and loperamide or nifuroxazide does not modify the kinetics of racecadotril.

4.6 Fertility, pregnancy and lactation

Pregnancy:
There are no adequate data from the use of racecadotril in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/ foetal development, parturition or postnatal development. However, since no specific clinical studies are available, racecadotril should not be administered to pregnant women.

Lactation:
Due to the lack of information on secretion of Hidrasec in human milk, the product should not be administered to breastfeeding women.

4.7 Effects on ability to drive and use machines

Racecadotril has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The following adverse drug reactions listed below have occurred with racecadotril more often than with placebo, or have been reported during post-marketing surveillance. The frequency of adverse reactions is defined using 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), very rare (< 1/10,000), not known (cannot be estimated from the available data).

Nervous system disorders
- Common: headache.

Skin and subcutaneous tissue disorders
- Uncommon: rash, erythema.
- Unknown: erythema multiforme, tongue oedema, face oedema, lip oedema, eyelid oedema, angioedema, urticaria, erythema nodosum, rash papular, prurigo, pruritus, toxic skin eruption.

A few cases of drowsiness have been reported during clinical trials. Nausea and vomiting, constipation, and dizziness have also been reported rarely. The side-effects have been mild, and equivalent in nature, frequency and intensity to those reported with placebo. Post marketing surveillance has indicated side-effects are extremely rare in general use.

Serious skin reactions (including angioedema) have been reported in patients on racecadotril therapy.
The incidence of these reactions is unknown but if they occur, racecadotril therapy must be discontinued and appropriate alternative therapy instituted. Patients should be aware not to take racecadotril again in these

cases.

4.9 Overdose

So far sporadic cases of overdose without adverse events have been reported. In adults, single doses above 2 g, which is equivalent to 20 times the therapeutic dose, have been administered and no harmful effects have been described. No specific antidote has been identified, and management should follow recognised procedures for overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

HIDRASEC is an inhibitor of enkephalinase, the enzyme responsible for breaking down enkephalins. It is selective but reversible inhibitor and protects endogenous enkephalins which are physiologically active in the digestive tract.

HIDRASEC has a pure intestinal antisecretory agent which has been shown to have no effect on gastrointestinal motility. It reduces intestinal hypersecretion of water and electrolytes caused by cholera toxin or inflammation without affecting basal secretion. There is therefore no effect in the normal intestine.

When given orally, enkephalinase inhibition is purely peripheral. HIDRASEC does not affect central nervous system enkephalinase activity, and has not been shown to produce habituation or central nervous stimulant or sedative effects.

5.2 Pharmacokinetic properties

Racecadotril is rapidly absorbed by the oral route. It is rapidly hydrolysed to (RS)-N-(-1-oxo-2-(mercaptomethyl)-3-phenylpropyl) glycine, its active metabolite, which is in turn converted into inactive metabolites which are eliminated through the kidneys, faeces and lungs.

The extent and duration of action of racecadotril depends on the dose administered.

Activity against plasma enkephalinase starts within thirty minutes, with peak activity corresponding to 75% inhibition for a dose of 100 mg, occurring 1-3 hours after administration. The biological half-life of racecadotril is 3 hours. For a dose of 100 mg the duration of activity against plasma enkephalinase is about 8 hours.

(RS)-N-(-1-oxo-2-(mercaptomethyl)-3-phenylpropyl) glycine, the active metabolite of racecadotril, is 90% bound to plasma proteins, mainly albumin. Tissue distribution only affects about 1% of the administered dose.

The pharmacokinetic properties of racecadotril are not changed by repeated administration or in elderly subjects. The bioavailability of racecadotril is not affected by food but the peak activity is delayed by one and a half hours.

5.3 Preclinical safety data

Chronic exposure in monkeys at a dose of 500 mg/kg/day resulted in generalized infections and reduced antibody responses to vaccination but no infection/immune depression was observed at 120 mg/kg/day. The clinical relevance of this finding is unknown.
Racecadotril was not immunotoxic in mice when given for up to 1 month.

Four-week toxicity studies in monkeys and dogs, relevant for the duration of treatment in patients, do not point out any effect at doses up to 1250 mg/kg/day and 200 mg/kg/day, respectively.

No mutagenic or clastogenic effect of racecadotril has been found in the standard *in vitro* and *in vivo* tests.

Reproductive and developmental toxicity studies have not revealed any special effects of racecadotril.

A toxicity study in juvenile rats has not revealed any significant effects of racecadotril up to a dose of 160 mg/kg/day which is 35 times higher than the usual paediatric regimen (i.e. 4.5 mg/kg/day).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

List of excipients :
Lactose monohydrate
Preglatinised maize starch
Magnesium stearate
Colloidal silicone dioxide
Capsule contains gelatin
Titanium dioxide (E171)
Yellow iron oxide (E172)

6.2 Incompatibilities

None known

6.3 Shelf life

The expiry date is indicated on the packaging

6.4 Special precaution for storage

Store below 30^0 C

6.5 Nature and contents of container

Hidrasec 100 mg capsule : Blister packs of 20 capsules in a carton

6.6 Instruction for Use/Handling
No further information of relevance

Hidrasec is a trade mark
HARUS DENGAN RESEP DOKTER

Packaging
Box, 2 blister of 10 capsules – Reg No. DKI1338700101A1

Manufactured by Laboratoires Sophartex, France
Imported by P.T Abbott Indonesia, Depok, Indonesia