1. NAME OF THE MEDICINAL PRODUCT

Hidrasec Infants Granules for Oral Suspension 10 mg
Hidrasec Children Granules for Oral Suspension 30 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet of Hidrasec Infants contains 10 mg of racecadotril.
Each sachet of Hidrasec Children contains 30 mg of racecadotril.

Excipients with known effect
Each sachet Hidrasec Infants contains 0.966 g of sucrose.
Each sachet Hidrasec Children contains 2.9 g of sucrose.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Granules for oral suspension.
White powder with apricot smell.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hidrasec Infants10mg, Hidrasec Children 30mg:
Complementary, symptomatic treatment of acute diarrhoea in infants (older than 3 months) and children, when oral rehydration and usual support measures are insufficient to control the clinical condition.

4.2 Posology and method of administration

Hidrasec Infants 10mg and Hidrasec Children 30mg are administered via the oral route, together with oral rehydration (see section 4.4).

Hidrasec Infants 10mg is intended for children < 13kg.
Hidrasec Children 30mg is intended for children ≥ 13kg.

The recommended dose is determined according to body weight: 1.5 mg/kg per dose (corresponding to 1 to 2 sachets), three times daily at regular intervals.
In infants less than 9 kg: one 10 mg sachet 3 times daily.
In infants from 9 kg to < 13 kg: two 10 mg sachets 3 times daily.

In children from 13 kg to 27 kg: one 30 mg sachet 3 times daily.
In children of more than 27 kg: two 30 mg sachets 3 times daily.

The duration of treatment in the clinical trials with children was 5 days. Treatment should be continued until two normal stools are recorded. Treatment should not exceed 7 days. Long term treatment with racecadotril is not recommended.

There are no clinical trials in infants under 3 months of age.

Special populations:
There are no studies in infants or children with renal impairment or hepatic impairment (see section 4.4).

Caution is advised in patients with hepatic or renal impairment.

The granules can be added to food, dispersed in a glass of water or in the feeding-bottle, mixing well and followed by immediate administration.

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.

Due to the presence of sucrose, Hidrasec Infants/Children is contraindicated in patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption syndrome or sucrase-isomaltase insufficiency.

4.4 Special warnings and precautions for use

The administration of Hidrasec does not modify usual rehydration regimens. Rehydration is highly important in the management of acute diarrhoea in infants. The requirement for rehydration and route should be adapted to the age and weight of the patient and the stage and severity of the condition, specifically in case of serious or prolonged diarrhoea with significant vomiting or a lack of appetite. Additionally, it is important that regular feeding (incl. breastfeeding) is not interrupted and that adequate fluid intake is monitored.

The presence of bloody or purulent stool and fever may indicate either 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.

Use of racecadotril in antibiotic-associated diarrhoea and chronic diarrhoea is not recommended due to insufficient data.

In patients with diabetes, it should be taken into account that each sachet contains:

- Hidrasec Infants: 0.966 g of sucrose
- Hidrasec Children: 2.899 g of sucrose

If the quantity of sucrose (source of glucose and fructose) present in the daily dose of Hidrasec exceeds 5 g a day, the latter should be taken into account in the daily sugar ration.

The product must not be administered to infants less than 3 months old, as there are no clinical trials in this population.

The product must not be administered to children with renal or liver impairment, whatever the degree of severity, due to a lack of information on these patient populations.

Because of possible reduced bioavailability, the product must not be administered in cases of prolonged or uncontrolled vomiting.

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 racecadontril. This may occur at any time during therapy.

Patients with a history of angioedema unrelated to racecadontril 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 of racecadotril with loperamide or nifuroxazide does not modify the kinetics of racecadotril.

4.6 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).

Infections and infestations:
Uncommon: tonsillitis.

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

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

Sporadic cases of overdose without adverse events have been reported in infants and children; ingested doses were up to 7 times the correct dose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antidiarrhoeals.
ATC code: A07XA04

Racecadotril is a prodrug that needs to be hydrolysed to its active metabolite thiorphan, which is an inhibitor of enkephalinase, a cell membrane peptidase located in various tissues, notably the epithelium of the small intestine. This enzyme contributes both to the hydrolysis of exogenous peptides and to the breakdown of endogenous peptides such as enkephalins. Consequently, racecadotril protects endogenous enkephalins that are physiologically active at the digestive tract level, prolonging their antisecretory effect.

Racecadotril is a pure intestinal antisecretory active substance. It decreases intestinal hypersecretion of water and electrolytes induced by cholera toxin or inflammation, and does not have effect on basal secretory activity. Racecadotril exerts rapid antidiarrhoeal action, without modifying the duration of intestinal transit.

In two clinical studies in children, racecadotril reduced by 40% and 46%, respectively, the stool weights in the first 48 hours. A significant reduction in the duration of the diarrhoea and the need for rehydration was also observed.

An individual patient data meta-analysis (9 randomised clinical trials racecadotril versus placebo, in addition to oral rehydration solution) collected individual patient data from 1384 boys and girls suffering from acute diarrhoea of miscellaneous severity and treated as in- or out-patients. The median age was 12 months (interquartile range: 6 to 39 months). A total of 714 patients were <1 year and 670 patients >1 year old. Mean weight ranged from 7.4 kg to 12.2 kg across studies. The overall median diarrhoea duration after inclusion was 2.81 days for placebo and 1.75 days for racecadotril. The proportion of recovered patients was higher in racecadotril groups compared with placebo [Hazard Ratio (HR): 2.04; 95% CI: 1.85 to 2.32; $p < 0.001$; Cox Proportional Hazards Regression]. Results were very similar for infants (<1 year) (HR: 2.01; 95% CI: 1.71 to 2.36; $p < 0.001$) and toddlers (> 1 year) (HR: 2.16; 95% CI: 1.83 to 2.57; $p < 0.001$). For inpatient studies (n = 637 patients), the ratio of mean stool output racecadotril/placebo was 0.59 (95% CI: 0.51 to 0.74); $p < 0.001$). For outpatient studies (n = 695 patients), the ratio of the mean number of diarhoeic stools racecadotril/placebo was 0.63 (95% CI: 0.47 to 0.85; $p < 0.001$).

Racecadotril does not produce abdominal distension. During its clinical development, racecadotril produced secondary constipation at a rate comparable to placebo.

When administered via the oral route, its activity is exclusively peripheral, with no effects on the central nervous system.

5.2 Pharmacokinetic properties

Absorption: Following oral administration, racecadotril is rapidly absorbed. The initial time to plasma enkephalinase inhibition is 30 minutes.

The bioavailability of racecadotril is not modified by food, but peak activity is delayed by about one hour and a half.

Distribution: In plasma, after an oral dose of 14C-labeled racecadotril, measured exposure of radiocarbon was many orders of magnitude higher than in blood cells and 3-fold higher than in whole blood. Thus, the drug did not bind to blood cells to any significant extent. Radiocarbon distribution in other body tissues was moderate, as indicated by the mean apparent volume of distribution in plasma of 66.4 kg.
Ninety percent of the active metabolite of racecadotril, thiorphan (= (RS)-N-(1-oxo-2-(mercaptomethyl)-3-phenylpropyl) glycine), is bound to plasma proteins, mainly to albumin.

The duration and extent of the effect of racecadotril are dose-dependent.

In children, time to peak enkephalinase inhibition is approximately 2 hours and corresponds to an inhibition of 90% with the dose of 1.5 mg/kg.

The duration of plasma enkephalinase inhibition is about 8 hours.

Metabolism: The biological half-life of racecadotril, measured as plasma enkephalinase inhibition, is approximately 3 hours.

Racecadotril is rapidly hydrolysed to thiorphan, the active metabolite, which is in turn transformed into inactive metabolites. In vitro data indicate that racecadotril/thiorphan and the four major inactive metabolites do not inhibit the major CYP enzymes isoforms 3A4, 2D6, 2C9, 1A2 and 2C19 to an extent that would be clinically relevant.

In vitro data indicate that racecadotril/thiorphan and the four major inactive metabolites do not induce the CYP enzymes isoforms (3A family, 2A6, 2B6, 2C9/2C19, 1A family, 2E1) and UGTs conjugating enzymes to an extent that would be clinically relevant.

Racecadotril does not modify protein binding of active substances strongly bound to proteins, such as tolbutamide, warfarin, niflumic acid, digoxin or phenytoin.

In the paediatric population, pharmacokinetic results are similar to those of the adult population, reaching C_{max} at 2 hours 30 min after administration. There is no accumulation after multiple doses administrated every 8 hours, for 7 days.

Excretion: Racecadotril is eliminated as active and inactive metabolites. Elimination is mainly via the renal route (81.4%), and to a much lesser extent via the faecal route (around 8%). The pulmonary route is insignificant.

5.3 Preclinical safety data

4-week toxicity studies in monkeys and dogs, relevant for the duration of treatment in human, do not point out any effect at doses up to 1250 mg/kg/day and 200 mg/kg, respectively corresponding to safety margins of 625 and 62 (vs human). Racecadotril was not immunotoxic in mice given for up to 1 month. Chronic exposure (1 year) in monkeys showed generalized infections and reduced antibody responses to vaccination at a 500 mg/kg/day

dose and no infection/immune depression at 120 mg/kg/day. Similarly in the dog receiving 200 mg/kg/day for 26 weeks some infection/immune parameters were affected. The clinical relevance is unknown (see section 4.8).

Preclinical effects (e.g. severe, most likely aplastic anaemia, increased diuresis, ketonuria, diarrhoea) were observed only at exposures considered sufficiently in excess of the maximum human exposure. The clinical relevance is unknown.

No mutagenic or clastogenic effect of racecadotril has been found in the standard *in vitro* and *in vivo* tests. Carcinogenicity testing has not been performed with racecadotril as the drug is provided for short-term treatment.

In animals, racecadotril reinforced the effects of butylhyoscine on bowel transit and on the anticonvulsive effects of phenytoin.

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 (ie 4.5 mg/kg/day).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sucrose, anhydrous colloidal silica, 30% polyacrylate dispersion, apricot aroma.

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years

6.4 Special precautions for storage
Store below 25°C.

6.5 Nature and contents of container
Thermo-welded paper/aluminium/polyethylene sachets.
Packs contain 10, 16, 20, 30, 50 or 100 sachets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

NAME AND ADDRESS OF MANUFACTURER
Laboratoires Sophartex
21 rue du Pressoir
28500 – Vernouillet
France

Date of last revision: 17 August 2017 (CCDS SOLID 1000301295 v5.0)