Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Hidrasec Infants and Children 4 mg/mL Oral Suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Racecadotril..... 4 mg

Each ml of oral suspension contains 4 mg of racecadotril

The 50 mL bottle contains 168 mg of racecadotril, corresponding to 112 kg-doses.

The 180 mL bottle contains 660 mg of racecadotril, corresponding to 440 kg-doses.

Each kg-dose corresponds to 1.5 mg/kg/dose.

Excipient(s) with known effect:

Each kg-dose of oral suspension contains: 1.13 mg of sodium benzoate, 0.84 mg of sodium, 225 mg of sucrose and 1.06 mg of propylene glycol.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Oral suspension.

White to off-white suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hidrasec Infants and Children 4mg/mL is indicated in addition to oral rehydration and dietary measures in the symptomatic treatment of acute diarrhoea in infants and children older than 3 months and weighing 7 kg and more, when oral rehydration and dietary measures alone are insufficient to control the clinical condition and where causal treatment is not possible.
If causal treatment is possible, racecadotril can be administered as a complementary treatment.

4.2 Posology and method of administration

Hidrasec Infants and Children 4mg/mL is administered via the oral route, together with oral rehydration (see section 4.4).

Posology

Paediatric population

Only for infants and children older than 3 months and weighing 7 kg to 52 kg

The usual dosage is based on child's body weight. It is 1.5 mg/kg/dose (which corresponds to one kg-dose).

On day one: a first dose immediately, then depending on the time of the first dose, up to a maximum of 3 doses spread over the day, including in these three doses the first dose immediately. The doses should preferably be administered at the beginning of the three main meals.

On the following days: 3 doses spread over the day, preferably at the beginning of the three main meals.

The maximum daily posology is 3 doses.

The medicinal product is administered orally using a syringe (graduated in kg of body weight) providing a dose 1.5 mg of racecadotril per graduation point indicated in kg.

For each dose:

- Infants and children up to 26 kg: fill the syringe up to the graduation point indicating the weight of the child.
- Children between 27 and 38 kg: fill the syringe once up to the 13 kg graduation point and administer the suspension to the child. Fill the syringe a second time until reaching a total that is the same as the child's weight and administer the suspension once again to the child.
- Children between 39 and 52 kg: fill the syringe once up to the 26 kg graduation point and administer the suspension to the child. Fill the syringe a second time until reaching a total that is the same as the child's weight and administer the suspension once again to the child.
- For weights exceeding 52 kg, please use the most suitable pharmaceutical forms.

Duration of treatment

The treatment should be continued until the return of two consecutive formed stools, without exceeding 7 days.
There are no clinical trials in infants fewer than 3 months of age.

Method of administration

Oral use.

1. Shake vigorously the bottle to mix the suspension prior to use
2. Open the bottle by twisting and pushing down on the child safety cap
3. Fully insert the syringe into the sampling tip
4. To fill the syringe, tip the bottle upside down. Hold the syringe securely in place and pull the plunger slowly and steadily to the required graduation point in kg
5. Place the bottle the right way up once again and remove the syringe
6. Insert the syringe without using force into the mouth of the child and administer all of the suspension while gently and gradually pushing down the plunger.

After each use, disassemble the oral syringe, rinse with water and dry. Use of this syringe for oral administration is strictly reserved for the administration of Hidrasec Infants and Children 4mg/mL.

Special populations:

No studies have been performed on children suffering from liver or kidney impairment (see section 4.4)

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Treatment with Hidrasec Infants and Children 4mg/mL is an adjuvant treatment to oral rehydration, and must not replace it. Rehydration should be systematic in infants/children with acute diarrhoea, to prevent or treat dehydration, and must be adapted to compensate for electrolyte losses.

Treatment of acute diarrhoea in infants/children is based primarily on correcting water and electrolyte losses through the use of oral rehydration salts and early refeeding, the methods of which are determined according to a child's age and the type of food consumed prior to the diarrhoea.

The requirement for rehydration by oral rehydration solution or intravenously should be adapted according to the severity of the diarrhoea, the age of the child and associated diseases.

In case of severe or prolonged diarrhoea, significant vomiting or the rejection of food, intravenous rehydration should be considered.

The presence of bloody or purulent stools and fever can be a sign of infectious diarrhoea or the presence of other ongoing conditions. In cases of infectious diarrhoea with clinical manifestations suggesting an invasive disease, the use of anti infectious agent with adequate systemic diffusion might be necessary.

Chronic diarrhoea has not been sufficiently studied with this product.

Racecadotril has not been evaluated in antibiotic-associated diarrhoea. As a result, racecadotril should not be used in these cases.

Due to potentially reduced bioavailability, racecadotril should not be administered in cases of prolonged or uncontrollable vomiting.
The product must not be administered to infants less than 3 months old, as there are no clinical trials in this population.

Excipients:

This medicinal product contains 225 mg/kg-dose of sucrose. This is to be taken into account for patients with diabetes mellitus.

Patients with fructose intolerance, glucose-galactose malabsorption syndrome or sucrase/isomaltase deficiency (rare hereditary diseases) should not take this medicine.

This medicinal product contains 0.84 mg of sodium per kg-dose.

The amount of sodium must be included in the maximum nutritional amount recommended by the WHO, corresponding to 1500 mg for children.

This medicinal product contains 1.13 mg of benzoate per kg-dose.

Renal and hepatic impairment:

Sodium benzoate may increase the risk of jaundice (yellowing of the skin and eyes) in newborns (up to 4 weeks).

This medicinal product contains 1.06 mg of propylene glycol per kg-dose.

Renal or hepatic impairment:

In cases of renal or hepatic impairment, Hidrasec Infants and Children 4mg/mL should not be administered due to the lack of data.

Hypersensitivity:

Skin reactions have been reported when using racecadotril. In most cases, these reactions are mild and do not require any treatment. However, in some situations, these reactions may be severe and life-threatening. Association with racecadotril cannot be entirely excluded. If severe skin reactions occur, racecadotril treatment should be halted immediately.

Cases of hypersensitivity and angioedema have been reported in patients treated with racecadotril. These events may occur at any time during treatment.

Angioedema of the face, extremities, lips and mucous membranes may occur.

When angioedema is associated with the obstruction of the upper airway, such as at tongue, glottis and/or larynx, emergency treatment should be administered immediately.

Racecadotril should be discontinued and the patient should be subjected to close medical supervision with initiation of appropriate monitoring until symptoms have completely and definitively disappeared. Racecadotril should not be reintroduced.

Bradykinin angioedema:

Racecadotril or some therapeutic classes are likely to cause a vascular reaction such as angioedema of the face and neck, resulting from the inhibition of the degradation of bradykinin.

The outcomes of angioedema can sometimes be fatal, due to airway obstruction. Angioedema can occur independently of a simultaneous association between these medicines if the patient has been previously exposed to one of the two protagonists. It will be necessary to search for the history of the occurrence of this effect and to determine the need for this type of association.

The combination of racecadotril with some medicinal products which increase the concentration of bradykinin, in particular Angiotensin-Converting Enzyme inhibitors (ACE) (eg perindopril and ramipril) increases the risk of causing bradykinin angioedema (see section 4.5).

Therefore, careful risk/benefit assessment is required before initiating the treatment with racecadotril in patients on Angiotensin-Converting Enzyme inhibitors (ACE) (see section 4.5).

Severe cutaneous adverse reactions (SCARs):
Severe cutaneous adverse reactions (SCARs) including drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported in association with racecadotril treatment. Patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of DRESS appear, racecadotril should be withdrawn immediately and an alternative treatment considered. If the patient has developed DRESS with the use of racecadotril, treatment with racecadotril must not be restarted in these patients at any time.

4.5 Interaction with other medicinal products and other forms of interaction

Drugs, Bradykinin and Angioedema

Certain drugs or classes of drugs may cause a vascular reaction such as angioedema of the face and neck, resulting from inhibition of bradykinin degradation. The most frequently implicated drugs are ACE inhibitors (e.g., perindopril, ramipril), and to a lesser extent: angiotensin II antagonists (e.g., candesartan, irbesartan), mTORi immunosuppressants, antidiabetic drugs of the gliptin class, racecadotril, estramustine, sacubitril and recombinant alteplase.

The consequences of angioedema can sometimes be fatal, due to airway obstruction. Angioedema may occur independently of a simultaneous combination of these drugs, if the patient has been previously exposed to either drug. A history of this effect should be sought and the need for such a combination assessed.

Not-recommended combinations (see also section 4.4)

Other drugs at risk of bradykinin angioedema (see section Drugs, Bradykinin and Angioedema)

4.6 Fertility, pregnancy and lactation

Pregnancy

Studies on animals have shown no direct or indirect harmful toxicity effects with respect to reproduction. The clinical data on the use of racecadotril during pregnancy is very limited. Consequently, Hidrasec Infants and Children 4mg/mL should not be administered during any stage of pregnancy.

Breast-feeding

In the absence of information on the transmission of racecadotril through breastmilk, and due to its pharmacological properties and the immaturity of the gastrointestinal tract in newborns, Hidrasec Infants and Children 4mg/mL should not be administered while breastfeeding.

Fertility

No effects on fertility have been observed in fertility studies in male and female rats.

4.7 Effects on ability to drive and use machines

Hidrasec Infants and Children 4mg/mL has no or a negligible effect on the ability to drive and use machines.

4.8 Undesirable effects

Clinical studies on Hidrasec sachets, another pharmaceutical form for infants and children during acute diarrhoea, provided usage safety data for 860 infants and children treated with racecadotril and for 441 treated with a placebo.

The adverse reactions listed below were observed more frequently with racecadotril than with the placebo in clinical studies or than were reported during the marketing period.

Adverse reactions are reported according to MedDRA primary system organ class. Within each system organ class, adverse reactions are ranked by frequency. Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness. The frequency of adverse reactions was defined using the following convention: very common (≥1/10), common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100), rare (≥ 1/10000 to <1/1000), very rare (<1/10000), unknown (cannot be estimated using the data available).

Severe cutaneous adverse reactions (SCARs) including drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported in association with racecadotril treatment (see section 4.4).

System Organ Class	Frequency	Adverse reactions
Infections and infestations	Uncommon	Tonsillitis
Skin and subcutaneous tissue disorders (see section 4.4)	Uncommon	rash, erythema
	Unknown frequency	urticaria, angioedema (Quincke's oedema) oedema of the tongue, face, lips, or eyelids, erythema multiforme, erythema nodosum, papular rash, pruritus, prurigo, toxicodermatitis, drug reaction with eosinophilia and systemic symptoms (DRESS)
Immune system disorder	Unknown	Anaphylactic shock

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 HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

In reported cases of overdose, patients presented no adverse reactions.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: INTESTINAL ANTI-DIARRHOEAL ANTI-SECRETORY.

ATC Code: A07XA04. (A: Digestive and metabolic).

Racecadotril is a pro-drug that must be hydrolysed to its active metabolite, thiorphan, which is an inhibitor of enkephalinase, the cell membrane enzyme present in various tissues, including the intestinal epithelium.

This enzyme contributes to the hydrolysis of exogenous and endogenous peptides such as enkephalins.

Racecadotril protects the enzymatic degradation of enkephalins, prolonging their action at enkephalinergic synapses in the small intestine, reducing hypersecretion.

Racecadotril is a pure intestinal antisecretory. It decreases the intestinal hypersecretion of water and electrolytes caused by cholera toxin or inflammation, without impacting on basal secretion. It performs antidiarrhoeal activity without altering transit time in the intestines.

In two clinical studies on children with presentations in sachets, racecadotril reduced the weight of stools in the first 48 hours by 40% and 46%, respectively.

A significant reduction in the duration of the diarrhoea and the need for rehydration was also observed.

A meta-analysis based on individual data (9 RCTs with sachets, racecadotril placebo plus oral rehydration solution) brought together the individual data of 1384 boys and girls suffering from acute diarrhoea of varying severity, who were treated as outpatients or inpatients.

The average age was 12 months old (interquartile range: 6 to 39 months old).

A total of 714 patients were less than 1 year old while 670 patients were over 1 year old. The average weight ranged from 7.4 kg to 12.2 kg, according to the studies. The overall mean duration of diarrhoea, post-inclusion, was 2.81 days in the placebo group 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 diarrhoeic 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.

A randomised, double-blind clinical study found that a therapeutic dose (one capsule) or higher dose (4 capsules) of racecadotril 100 mg did not cause the prolongation of QT/QTc in 56 healthy adult volunteers (unlike the effect observed with moxifloxacin, used as a positive control).

5.2 Pharmacokinetic properties

Absorption

Following oral administration, racecadotril is rapidly absorbed. The activity on plasma enkephalinase appears from the thirtieth minute.
Although the bioavailability of racecadotril is not modified by food, peak activity is delayed for approximately 1 hour and a half.

Distribution

Following the oral administration of 14C-labelled racecadotril in healthy volunteers, the concentration of racecadotril was approximately 200 times higher in plasma than in blood cells and about 3 times greater in plasma than in the total volume of blood. Racecadotril does not bind significantly to blood cells.

In plasma, the apparent mean volume of distribution of 66.4 L/kg demonstrated a moderate distribution of 14C in other tissues.

Ninety percent of tiorphan, (RS) -N- (1-oxo-2- (mercaptomethyl) -3-phenylpropyl) glycine, the active metabolite in racecadotril, is bound to plasma proteins, mainly albumin.

The pharmacokinetic properties of racecadotril are not changed during repeated administration or in the elderly.

The amplitude and duration of action of racecadotril are related to the administered dose. The peak concentration is about 2 hours and 30 minutes, corresponding to a 90% inhibition of enzymatic activity for the administered dose of 1.5 mg/kg.

For a 100 mg dose, the duration of activity in plasma enkephalinase is about 8 hours.

Metabolism

The biological half-life of racecadotril, determined from plasma enkephalinase inhibition, is 3 hours.

Racecadotril is rapidly hydrolysed in thiorphan (RS) -N- (1-oxo-2- (mercaptomethyl) -3-phenylpropyl) glycine, its active metabolite, which is itself transformed into the inactive metabolites S-methylthiorphan sulfoxide, methyl TIORFAN S, 2-methanesulfinylmethyl propionic acid and 2-methylsulfanylmethyl propionic acid, which were formed at more than 10% of the systemic exposure of the parent compound.

Other minor metabolites were also detected and quantified in urine and faeces. The repeated administration of racecadotril does not cause its accumulation in the body.

In vitro data shows that racecadotril/thiorfan and their four major inactive metabolites do not act significantly as inhibitors of the CYP3A4, 2D6, 2C9, 1A2 and 2C19 isoforms.

In vitro data shows that racecadotril/thiorfan and four major inactive metabolites do not act significantly as inducers of cytochrome CYP isoforms (family 3A, 2A6, 2B6, 2C9/2C19, family 1A, 2E1) and enzymes that bind to glucuronyl transferase.

Racecadotril does not alter the protein binding of highly protein-bound products, such as tolbutamide, warfarin, niflumic acid, digoxin or phenytoin.

In patients with hepatic impairment (cirrhosis, Child-Pugh B), the pharmacokinetic profile of the metabolite displays the same Tmax and T1/2 and a lower Cmax (-65%), as well as the same area under the curve (-29%), compared to healthy subjects.

In patients with severe renal impairment (creatinine clearance between 11 and 39 mL/min), the pharmacokinetic profile of the metabolite presents a lower Cmax (-49%) and a greater area under the curve (+15%) and T1/2, compared to healthy subjects (creatinine clearance w> 70 mL/min).

In the pediatric population, the pharmacodynamic results are similar to those of the adult population, with a Cmax occurring 2 hours and 30 minutes after administration. There is no accumulation after repeated doses every 8 hours for 7 days.

Excretion

Racecadotril is eliminated through its active and inactive metabolites. Elimination occurs mainly via the kidneys (81.4%), and to a lesser extent in the faeces (about 8%). Pulmonary excretion is not significant (less than 1% of the dose).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, or toxicity to reproduction and development.

Four-week chronic toxicity studies performed in monkeys and dogs, which are useful for the assessment of the duration of treatment in humans, showed no major effect at doses up to 250 mg/kg/day and 200 mg/kg/day, respectively. Available corresponding toxicokinetics corresponds to a safety margin of 21 in monkeys (compared to the recommended paediatric dose, i.e., 4.5 mg/kg/day). At higher doses, profuse diarrhoea, vomiting, ketonuria and anaemia were main preclinical adverse findings with no known clinical relevance.

A 1-year toxicity study in monkeys showed significant mortality resulting from infections and a reduced response of antibodies to vaccination (at a dose of 500 mg/kg/day) and no adverse effects including infection/immunosuppression at 150 mg/kg/day. In the absence of corresponding toxicokinetics data, safety margins based on body surface area conversion to a human equivalent dose (HED) of this NOAEL is of at least 10 compared to the recommended paediatric dose.

Similarly, in dogs treated at the single dose of 200 mg/kg/day for 26 weeks, some infectious/immune reactions including anaemia and thrombocytopenia were detected allowing no safety margin calculations. The clinical relevance of these findings is unknown.

Racecadotril did not display immunotoxicity in mice treated for 1 month.

Carcinogenicity tests were not carried out since this is a short-term treatment.

A toxicity study in juvenile rats (aged from postnatal day 4-42) did not evidence any significant effects of racecadotril up to doses of 500 mg/kg/day, corresponding to a safety margin of 63 (compared to the recommended paediatric dose).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium benzoate, hydroxyethylcellulose, xanthan gum, sucrose, sodium citrate, lactic acid (for pH adjustment), strawberry flavour*.

* Composition of strawberry flavour: flavouring compounds, flavouring compounds of natural origin and propylene glycol.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Before opening the bottle: 24 months

After first opening of the bottle: 10 days.

6.4 Special precautions for storage

Store at a temperature not exceeding 25°C.

6.5 Nature and contents of container

50 mL bottle (PET) with child-resistant cap (PE) and a 10 mL syringe, graduated in kg, for oral administration. Box of 1 bottle containing 112 kg-doses.

180 mL bottle (PET) with child-resistant cap (PE) and a 10 mL syringe, graduated in kg, for oral administration. Box of 1 bottle containing 440 kg-doses.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with the regulations in force

7 MARKETING AUTHORISATION HOLDER

Bioprojet Pharma
9 Rue Rameau
75002 Paris
France

8 MARKETING AUTHORISATION NUMBER

PA22580/002/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25th November 2022

10 DATE OF REVISION OF THE TEXT

May 2024