

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

HIDRASEC INFANTS 10 mg, Granules for oral suspension.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains 10 mg of racecadotril.

Each sachet contains 966.5 mg of sucrose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Granules for oral suspension.

White powder with characteristic apricot smell

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Complementary symptomatic treatment of acute diarrhoea in infants (older than 3 months) and children together with oral rehydration (ORS).

If causal treatment of acute diarrhea is possible, racecadotril can be co-administered.

4.2 Posology and method of administration

Hidrased 10 mg is administered via the oral route, together with oral rehydration (see section 4.4). Hidrasec Infants is intended for children <13 kg

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 infant less than 9 kg : one 10 mg sachet 3 times daily.

In infant from 9 kg to 13 kg : two 10 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.

Paediatric population

There are no clinical trials to support treatment in infants less than 3 months old.

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

Method of administration

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 listed in section 6.1.

This medicinal product contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption syndrome or saccharase-isomaltase deficiency should not take this medicine.

4.4 Special warnings and precautions for use

Rehydration (including vomiting and diarrhoea)

The administration of Hidrasec does not modify the 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

In the event of serious or prolonged diarrhoea with important vomiting or a lack of appetite, intravenous rehydration should be considered.

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. Also, racecadotril has not been tested in antibiotic-associated diarrhoea. Therefore, racecadotril should not be administered under these conditions.

Chronic diarrhoea has not been sufficiently studied with this product.

Hypersensitivity

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.

Angioedema

Angioedema of the face, extremities, lips, mucous membranes may occur during racecadotril treatment.

This angioedema can be allergic (mast cell mediator-induced angioedema), or non-allergic (bradykinin-mediated angioedema). The combination of racecadotril with medicinal products which increase the concentration of bradykinin, in particular Angiotensin-Converting Enzyme (ACE) inhibitors, increases the risk of bradykinin-mediated angioedema (see section 4.5). Therefore, a careful risk/benefit assessment is required before initiating the treatment with racecadotril in patients on ACE inhibitors (see section 4.5).

If upper airway obstruction, emergency therapy should be administered promptly whatever the aetiology of angioedema, as the outcome of this condition can be fatal.

If angioedema occurs, racecadotril should be discontinued, and the patient should be under close medical supervision until complete and sustained resolution of symptoms. Racecadotril should not be reintroduced.

Renal or hepatic impairment

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.

Excipients

In patients with diabetes, it should be taken into account that each sachet contains 0.966 g of sucrose.

If the quantity of sucrose (source of glucose and fructose) present in the daily dose of Hidrasec 10 mg exceeds 5 g a day, the latter should be taken into account in the daily sugar ration.

4.5 Interaction with other medicinal products and other forms of interaction

Bradykinin-mediated 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, and to a lesser extent: angiotensin II antagonists, mammalian target of rapamycin inhibitors (mTORi) immunosuppressants, antidiabetic drugs of the gliptin class, racecadotril, estramustine, sacubitril and recombinant alteplase.

Concomitant use of racecadotril and other drugs known to cause bradykinin-mediated angioedema may increase the risk of angioedema and are not recommended (see section 4.4).

4.6 Fertility, pregnancy and lactation

Fertility:

Fertility studies conducted with racecadotril on Rats demonstrate no impact on fertility.

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, fertility, embryo- foetal development, childbirth/ delivery 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 regarding racecadotril excretion in human milk, this medicinal product should not be administered to breastfeeding women.

4.7 *Effects on ability to drive and use machines*

Not relevant.

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

4.8 Undesirable effects

Data from clinical acute diarrhoea studies are available for 860 paediatric patients treated with racecadotril, and 441 treated with placebo.

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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ 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: (See section 4.4)

- Uncommon: rash, erythema.
- Unknown: erythema multiforme, tongue oedema, face oedema, lip oedema, eyelid oedema, angioedema, urticaria, erythema nodosum, rash papular, prurigo, pruritus.

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 Yellow Card Scheme,

Website: www.mhra.gov.uk/yellowcard

4.9 Overdose

No cases of overdose 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antidiarrhoeals.

ATC code: A07XA04.

Racecadotril is a pro-drug that needs to be hydrolysed to its active metabolite thiorphan, which is an inhibitor of enkephalinase, a cell membrane peptidase enzyme located in various tissues, notably the epithelium of the small intestine. This enzyme contributes both to the digestion of exogenous peptides and to the breakdown of endogenous peptides such as enkephalins.

Racecadotril protects enkephalins from enzymatic degradation thereby prolonging their action at enkephalinergic synapses in the small intestine and reducing hypersecretion

Racecadotril is a pure intestinal antisecretory active substance. It decreases the intestinal hypersecretion of water and electrolytes induced by the cholera toxin or inflammation, and does not have effects 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 were ≥ 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 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 randomized crossover study demonstrated that racecadotril 100mg capsule at therapeutic dose (1 capsule) or at supratherapeutic dose (4 capsules) did not induce QT/QTc prolongation in 56 healthy volunteers (at the opposite of moxifloxacin, used as a positive control).

5.2 Pharmacokinetic properties

Absorption: following oral administration, racecadotril is rapidly absorbed.

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) glycin), is bound to plasma proteins, mainly to albumin.

Pharmacokinetics properties of Racecadotril are not modified in case of repeated administration.

The duration and extent of the effect of racecadotril are dose-dependent. Time to peak plasma 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 half-life of racecadotril, measured as plasma enkephalinase inhibition, is approximately 3 hours.

Racecadotril is rapidly hydrolysed to thiorphan (RS)-N-(1-oxo-2-(mercaptomethyl)-3-phenylpropyl) glycin, the active metabolite, which is in turn transformed into inactive metabolites identified as sulfoxide of S-methylthiorphan, S-methyl thiorphan, 2-methanesulfinylmethyl propionic acid and 2-methylsulfonylmethyl propionic acid, which all were formed at greater than 10% of parent drug systemic exposure.

Additional minor metabolites were also detected and quantified in urine and faeces.

Repeated administration of Racecadotril does not cause any accumulation in the body.

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.

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 dose administered 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 not significant (less than 1% of the dose).

5.3 Preclinical safety data

Chronic 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 racecadotril for up to 1 month. Longer 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.

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.

Reproductive and developmental toxicity (fertility and early embryonic development, prenatal and postnatal development including maternal function, embryo-foetal development 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 160mg/kg/day which is 35 times higher than the usual paediatric regimen (ie 4.5mg/kg/day).

Despite the immature renal function in children below 1 year of age, higher exposure levels are not expected in these individuals.

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

Other safety pharmacology studies did not evidence any deleterious effects of racecadotril on the central nervous system, the cardiovascular and the respiratory functions.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose,
Anhydrous colloidal silica,
polyacrylate dispersion 30 per cent,
Apricot aroma.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 *Nature and contents of container*

Thermowelded paper/aluminium/polyethylene sachets.

Packs containing 10, 16, 20, 30, 50 and 100 sachets (100 sachets only for hospital use).

Not all pack sizes may be marketed.

6.6 *Special precautions for disposal and other handling*

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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EI-DUBLIN 5

IRELAND

8 MARKETING AUTHORISATION NUMBER(S)

PL 39418/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

03/01/2016

10 DATE OF REVISION OF THE TEXT

02/01/2025