SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

HIDRASEC 175mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Racecadotril……175 mg

For each film-coated tablet.

Excipients of known effects:

Each tablet contains 139.6 mg (0.4mmol) of lactose anhydrous equivalent to 144.1mg of lactose monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

White film-coated tablet without marking.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hidrasec is indicated for the symptomatic treatment of acute diarrhoea in adults when 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

Posology

For adults only.
The first day: one tablet straightaway regardless of the time of day, then, depending on the time of the first intake, up to a maximum of 2 tablets spread over the day, counting in these 2 tablets the first tablet taken straightaway. Taken should preferably be done before meals.
The following days: one tablet in the morning and one tablet in the evening, i.e. 2 tablets per day, preferably before meals.
Treatment should be continued until two normal stools are recorded.
Treatment should not exceed 7 days.

Special populations:
Paediatric population:
The safety and efficacy of racecadotril 175 mg film-coated tablets in children and adolescents have not been established. No data are available. More appropriate formulations of racecadotril indicated for use in paediatric patients, such as granules in sachet, should be used.

Elderly:
Dosage adjustment is not necessary in the elderly person (see section 5.2). Caution is advised in patients with hepatic or renal impairment.

Method of administration

Oral route. Swallow with a glass of water.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

The administration of Hidrasec 175mg does not modify the usual rehydration regimens and dietary measures.
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 assessed in antibiotic-associated diarrhoea, therefore racecadotril should not be administered under these conditions
Chronic diarrhoea has not been sufficiently studied with this medicinal product.
There is a possible reduced bioavailability in patients with prolonged vomiting.

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

Excipients :
This medicinal product contains 139.6 mg (0.4 mmol) of lactose anhydrous. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Hypersensitivity:
Occurrence of skin reactions has been reported with the use of the product. In most cases, these are mild and do not require treatment. However, 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/Angioneurotic Oedema have been reported in patients with racecadotril. This may occur at any time during therapy.
Angioedema of the face, extremities, lips, mucous membranes may occur.
Where there is angioedema associated with upper airway obstruction, such as tongue, glottis and/or larynx, emergency therapy should be administered promptly.
Racecadotril should be discontinued and the patient should be under close medical supervision with appropriate monitoring initiated and continued until complete and sustained resolution of symptoms has occurred. 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).

Others
In humans, 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, 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.

Breast-feeding

Due to the lack of information about the excretion of racecadotril in human milk, Hidrasec 175mg should not be administered to breastfeeding women.

Fertility

Fertility studies conducted with racecadotril on male and female rats demonstrate no impact on fertility.

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

As part of clinical acute diarrhoea studies, data are available for 2193 adult patients treated with racecadotril and 282 treated with placebo.
The following adverse effects listed below have occurred with racecadotril more often than with placebo, or have been reported during post-marketing surveillance.

Tabulated list of adverse reactions
Adverse reactions reported are presented in table below. Adverse reactions are listed 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 convention: very common (≥1/10), common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100), not known (cannot be estimated from the available data).

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
Nervous system disorders	Common	headache
Skin and subcutaneous tissue disorders	uncommon	rash, erythema
	not known	erythema multiforme, tongue oedema, face oedema, lip oedema, eyelid oedema, angioedema, urticaria, erythema nodosum, rash papular, prurigo, pruritus, toxic skin eruption, drug reaction with eosinophilia and systemic symptoms (DRESS)
Immune system disorder	Not known	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 the Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

4.9 Overdose

In adults, single doses above 2g, 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 antidiarrhoea - 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 and endogenous peptide 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 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.

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

When administered by oral route, its activity is exclusively peripheral, without any effects on the central nervous system.

A randomized crossover study demonstrated that racecadotril 100mg at therapeutic dose (1 capsule) or at a higher dose (4 capsules) don't induce QT/QTc prolongation in 56 healthy volunteers (at the opposite of moxifloxacin, used as a positive control).

Clinical efficacy:

The racecadotril 175 mg film-coated tablet, administered twice daily (T=175, ntotal= 227), and 100mg capsules administered three times daily (C100, ntotal=229), were compared for the symptomatic treatment of acute diarrhoea in adults, in 2 randomized studies (P05-12, and P04-02).

In study P05-12, the mean number of stools in the last 24 hour prior to inclusion was 5 in the T175 (n= 117) and 5.5 in the C100 (n= 118) treatment group. The mean duration of diarrhoea up to inclusion was 29.5 and 29.3 hours in respective treatment groups.

In study P04-02, the mean number of stools in the last 24 hour prior to inclusion was 5.2 in the T175 (n= 110) and 5.3 in the C100 (n= 111) treatment group. The mean duration of diarrhoea up to inclusion was 32.6 and 31.3 hours in respective treatment groups.

The following table provides the mean number of diarrheic stools (NDS, main endpoint) and the median duration of the diarrheic (DD) episode from inclusion until recovery for each study and treatment arm:

	P05-12 Study		P04-02 Study	
	Mean NDS	Median DD (hour)	Mean NDS	Median DD (hour)

C100	6	33	6.2	17.5
T175	4	24	4	13.7

A meta-analysis on the 2 studies was performed: from an observed mean baseline number of diarrhoeic stools (NDS) in the last 24 hours prior to inclusion of 5.96, observed mean NDS from inclusion until recovery was 4 in T175-treated patients (n_{total}= 227) and 6 in C100-treated patients (n_{total}= 229) (difference= -2.0 [p25-p75: -3.21, - 0.78] (P<0.001)

The median DDs from inclusion until recovery were respectively 20h (T175) and 26h (C100) with a T175/C100 hazard ratio of 0.73 [95% CI: 0.60-0.88], p=0,001). Hence, diarrhoea resolved more quickly in T175-treated patients compared to C100-treated patients.

5.2 Pharmacokinetic properties

Absorption

With oral route, racecadotril is quickly absorbed. The exposure at steady state is comparable with the exposure following a single dose.Racecadotril bioavailability is not modified by food, but peak activity is delayed by about one hour and a half.

Distribution

After oral administration of 14C-labeled racecadotril in healthy volunteers, racecadotril concentration was more than 200 times higher in plasma than in blood cells and 3 times higher in plasma than in total 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 L/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.

Racecadotril pharmacologic properties are not modified by repeat dose or administration to elderly person. The duration and extent of the effect of racecadotril are dose-dependent. Time to peak plasma enkephalinase is approximately 2 hours and corresponds to 75% inhibition with the dose of 100 mg.

With a dose of 100 mg, the duration of plasma enkephalinase is about 8 hours.

Biotransformation

Racecadotril biological half-life, measured with plasma enkephalinase inhibition, is approximately 3 hours. Racecadotril is quickly hydrolysed to thiorphan (RS)-N-(1-oxo-2-(mercaptomethyl)-3-phenylpropyl) glycine, its active metabolite, which is in turn transformed into inactive metabolites identified as sulfoxyde of S-methylthiorphan, S-methyl thiorphan, 2-methanesulfinylmethyl propionic acid and 2-methylsulfanylmethyl 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.

Repeat 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 significantly 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 significantly 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 patients with liver failure [cirrhosis, grade B of the Child-Pugh classification], the kinetic profile of the racecadotril active metabolite showed similar Tmax and T½ and lower Cmax (-65%) and AUC (-29%) as compared to healthy subjects.

In patients with severe renal failure (creatinine clearance 11-39 ml/min), the kinetic profile of the racecadotril active metabolite showed a lower Cmax (-49%) and higher AUC (+16%) and T½ as compared to healthy volunteers (creatinine clearance >70 ml/min).

In the paediatric population, pharmacokinetic results are similar to those of the adult population, reaching Cmax at 2 hours 30 min after administration. There is no accumulation after multiple dose 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 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 humans, do not point out any effect at doses up to 1250 mg / kg / day and 200mg/kg, respectively corresponding to safety margin of 625 and 62 (vs human).

Racecadotril was not immunotoxic in mince given racecadotril for up to 1 month.

Longer exposure (1 year) in monkeys showed generalized infections and reduced antibody responses to vaccination at 500 mg / kg / day dose and no infection / immune depression at 120 mg / kg / day.

Similarly, in dogs receiving 200 mg / kg / day for 26 weeks, some infection / immune parameters were affected. Their clinical relevance is unknown: refer to section 4.8.

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

Carcinogenicity testing has not been performed with racecadotril as the drug is provided for short-term treatment.

Reproductive and development toxicity (fertility ans early embryonic development, pre-natal and postnatal development, including maternal function embryo-fetal development studies) revealed no special effect of racecadotril.

Other preclinical effects (e.g, severe aplastic anemia, increased diuresis, ketonesuria, diarrhea) were observed only at exposures considered sufficiently in excess of the maximum human exposure.

Their clinical significance is unknown.

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

In animals, racecadotril reinforced the effects of butylhyoscine upon bowel transit and the anticonvulsive effect of phenythoïne.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:

Lactose monohydrate

Calcium carmellose

Hydroxypropylcellulose

Cellulose microcrystalline

Pregelatinised starch (maize)

Magnesium stearate

Coating:

OPADRY white (polyvinyl alcohol, titanium dioxide, macrogol 3350, talc)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

4 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

3, 6 or 12 film-coated tablets (PVC-PVDC/ Aluminium blister).
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

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

7 MARKETING AUTHORISATION HOLDER

BIOPROJET PHARMA

9, rue rameau

75002 Paris

FRANCE

8 MARKETING AUTHORISATION NUMBER(S)

PL 26351/0004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19/09/2018

10 DATE OF REVISION OF THE TEXT

24/04/2024