

SUMMARY OF PRODUCT CHARACTERISTICS

Tiorfan Hidrasec Tiorfix Tiorfast 100 mg

1. NAME OF THE MEDICINAL PRODUCT

TIORFAN 100 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 100 mg of racecadotril.

Excipients: Each capsule contains 41 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule, hard.

Ivory coloured capsules. Size 2, containing a white powder with a sulphur odor.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TIORFAN 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

For oral use.

Adults:

One capsule initially regardless of the time of day. Then, one capsule three times daily preferably before the main meals. Treatment should be continued until two normal stools are recorded.

Treatment should not exceed 7 days.

Long-term treatment with racecadotril is not recommended.

Special populations:

Children: There are specific formulations intended for infants, children and adolescents.

Elderly: Dosage adjustment is not necessary in the elderly (see section 5.2).

Caution is advised in patients with hepatic or renal impairment.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

Precautions for use:

The administration of racecadotril 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. Therefore, racecadotril should not be administered under these conditions.

Chronic diarrhoea has not been sufficiently studied with this medicinal product. Also, racecadotril has not been tested in antibiotic associated diarrhoea.

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.

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4.5 Interaction with other medicinal products and other forms of interaction

To date, no interactions with other medicinal products have been described in humans.

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

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, parturition or postnatal development. However, since no specific clinical studies are available, racecadotril should not be administered to pregnant women.

Lactation:

There is insufficient information on the excretion of racecadotril in human milk; this medicinal 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

Data from clinical acute diarrhoea studies are available for 2193 adult patients treated with racecadotril and 282 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).

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.

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 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

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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 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 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: After oral administration of ¹⁴C-labeled racecadotril in healthy volunteers, racecadotril concentration was more than 200 fold higher in plasma than in blood cells and 3-fold 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 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. Time to peak plasma enkephalinase inhibition 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 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 (RS)-N-(1-oxo-2-(mercaptomethyl)-3-phenylpropyl) glycine, the 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-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.

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 active metabolite of racecadotril showed similar Tmax and T½ and lesser 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

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active metabolite of racecadotril showed smaller C_{max} (-49%) and greater AUC (+16%) and T_{1/2} 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 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) revealed no special effects of racecadotril.

Other 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. 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

Powder

Lactose monohydrate

Pregelatinised starch (maize)

Magnesium stearate

Silica Colloidal anhydrous

Capsule

Yellow iron oxide (E172)

Titanium dioxide (E171)

Gelatin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

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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

PVC-PVDC/ Aluminium blister.

Packs containing 6, **10**, 20, and 100 capsules (Hospital use) and 500 capsules (Hospital use).

Not all pack sizes may be marketed

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

To be completed nationally

8. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: (to be completed nationally)

Date of first Renewal of the authorisation: June 4, 2007

10. DATE OF REVISION OF THE TEXT

To be completed nationally

<11. DOSIMETRY>

Not applicable

<12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS>

Not applicable