SECADRIL™
(Racecadotril)

10mg & 30mg Sachet
100mg Capsule

سیکاڈرل
(ریسیکاڈوٹرل)

۱۰ ملی گرام ، ۳۰ ملی گرام ساشے
۱۰۰ ملی گرام کیپسول

QUALITATIVE AND QUANTITATIVE COMPOSITION

Secadril 10mg Sachets:
Each sachet contains: Racecadotril B.P. 10mg
Innovator's Specification

Secadril 30mg Sachets:
Each sachet contains: Racecadotril B.P. 30mg
Innovator's Specification

Secadril 100mg Capsules:
Each Capsule contains: Racecadotril B.P. 100mg
Innovator's Specification

DESCRIPTION

Racecadotril (acetorphan) is an oral enkephalinase inhibitor for use in the treatment of acute diarrhea. By preventing the degradation of endogenous enkephalins, racecadotril reduces hypersecretion of water and electrolytes into the intestinal lumen.

CLINICAL PHARMACOLOGY

Pharmacodynamics: Racecadotril is a pro-drug that needs to be hydrolysed to its active metabolite thiorphan, which is an inhibi-tor 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 antidiarrheal action, without modifying the duration of intesti-nal 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 addi-tion to oral rehydration solution) collected individual patient data from 1384 boys and girls suffering from acute diarrhea 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 2.81days 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 inpa-tient 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 diarrheic 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 cap-sule) 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).

Pharmacokinetics:

Absorption: Following oral administration, racecadotril is rapidly absorbed. The exposure at steady state is comparable with the exposure following a single dose.

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) glycin), is bound to plasma proteins, mainly to albumin. The duration and extent of the effect of racecadotril are dose dependent. Time to peak plasma enkephalin-ase 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 approximately 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 sulfoxyde of Smethylthiorphan, Smethyl thiorphan, 2-methanesulfinyl-methyl 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. 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 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 signifi-cant (less than 1% of the dose).

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 safe-ty 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 re-sponses 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 af-fected. 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 spe-cial 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 (i.e. 4.5mg/kg/day). Despite the immature renal function in children below 1 year of age, higher exposure levels are not ex-pected in these individuals. Other preclinical effects (e.g., severe, most likely aplastic anaemia, increased diuresis, ketonuria, diarrhea,) were observed only at exposures considered sufficiently in excess of maximum human exposure. Their clini-cal 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.

INDICATIONS

Complementary symptomatic treatment of acute diarrhoea in infants (older than 3 months) and in children together with oral rehydration and the usual support measures, when these measures alone are insufficient to control the clinical condition, and when causal treatment is not possible.

If causal treatment is possible, racecadotril can be administered as a complementary treatment.

CONTRAINDICATIONS

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

INTERACTIONS

Interaction of racecadotril with ACE inhibitors: Concomitant use of racecadotril and ACE inhibitors (e.g. captopril, enalapril, lisinopril, perindopril, ramipril) may increase the risk of angioedema. In humans, joint treatment with racecadotril and loperamide or nifuroxazide does not modify the kinetics of racecadotril.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Precautions for use: The administration of Hidrasec Children 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 an-tibiotic-associated diarrhoea. Therefore, racecadotril should not be administered under these conditions. Chronic diarrhoea has not been sufficiently studied with this product.

Warnings: In patients with diabetes, it should be taken into account that each sachet contains 2.899 g of sucrose. If the quantity of sucrose (source of glucose and fructose) present in the daily dose of Hidrasec Children 30 mg exceeds 5g 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/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 appro-priate monitoring initiated and continued until complete and sustained resolution of symptoms has oc-curred. Patients with a history of angioedema unrelated to racecadotril therapy may be at increased risk of angi-oedema. Concomitant use of racecadotril and ACE inhibitors may increase the risk of angioedema (see section 4.5). Hence, a careful benefit-risk assessment is needed before initiating treatment with racecadotril in patients on ACE inhibitors.

USE IN SPECIFIC POPULATION

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 indi-cate 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, Hid-rasec 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.

ADVERSE REACTIONS

Data from clinical acute diarrhoea studies are available for 860 paediatric patients treated with racecado-tril, 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 (_ 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, rash papular, prurigo, pruritus.

DOSAGE AND ADMINISTRATION

Hidrasec Children is administered via the oral route, together with oral rehydration. Secadril 30mg 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 children from 13kg to 27kg: One 30mg sachet 3 times daily.

In children of more than 27kg: Two 30mg sachets 3 times daily.

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

Special populations:

Infants and children: There are no studies in infants or children with renal impairment or hepatic impairment.

Hepatic and renal impairment: 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.

Dasage: As directed by the physician.

Instructions: Store below 30°C. Protect from heat, light and moisture. Keep all medicines out of the reach of childern. Treatment should not exceed 7 days. Oral use with oral rehydaration.

Direction for use: The granules should be added to food or mixed with water in a glass or baby bottle-Mix well and give immediately to your child.

PRESENTATION

Secadril 10mg Sachets:

Secadril (Racecadotril) 10mg Sachet are available in sixteen sachets (1 x 16's) in a carton.

Secadril 30mg Sachets:

Secadril (Racecadotril) 30mg Sachet are available in ten sachets (1 x 10's) in a carton.

Secadril 100mg Capsules:

Secadril (Racecadotril) 10mg Capsules are available in one Alu-Pvc blister of ten capsules (1 x 10's) in a carton.

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات: ۳۰ ڈگری سینٹی گریڈ سے کم پر رکھیں۔ روشنی، گرمی اور نمی سے محفوظ رکھیں۔

تمام دوائیں بچوں کی پہنچ سے دور رکھیں۔ دوا کا دورانیہ ۷ دن سے زیادہ نہ رکھیں۔

طریقہ استعمال: گرینیولز غذا یا پانی میں یا بچے کی بوتل میں ملائیں اور فوراً اپنے بچے کو دیں۔

For detailed information:

Genix Pharma (Pvt.) Ltd.

44,45-B, Korangi Creek Road, Karachi-75190, Pakistan.

UAN: +92-21-111-10-10-11, **Email:** info@genixpharma.com

www.genixpharma.com

ISO 9001:2015 ISO 14001:2015 ISO 45001:2018