For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

Zedott Kid

(Racecadotril 30mg Sachet I.P.)

COMPOSITION

Each sachet contains:

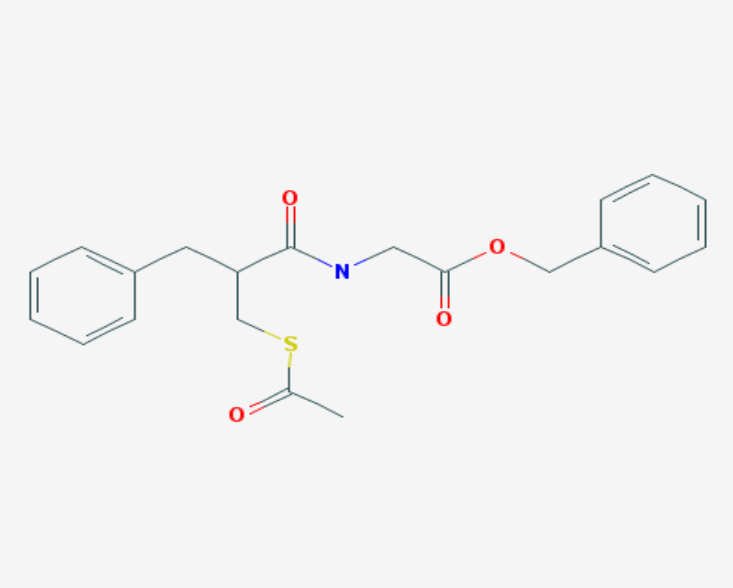
Racecadotril I.P. 30mg

Excipients q.s.

Colour: Sunset Yellow FCF

DESCRIPTION

Racecadotril is chemically (±)-*N*-{2-[(Acetylthio)methyl]-1-oxo-3-phenylpropyl}glycine phenylmethyl ester; N-[(R,S)-3-acetylthio-2-benzylpropanoyl]glycine benzyl ester; (±)-*N*-[α-(Mercaptomethyl)hydrocinnamoyl]glycine benzyl ester acetate. It is having the empirical formula of $C_{21}H_{23}NO_4S$ with molecular weight of 385.5. Racecadotril is an enkephalinase inhibitor that inhibits the breakdown of endogenous opioids, thus reducing intestinal secretions.



CLINICAL PHARMACOLOGY

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 2.81days 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 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.

Pharmacokinetic

Absorption: following oral administration, racecadotril is rapidly absorbed.

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 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 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, 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.
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 significant (less than 1% of the dose).

INDICATIONS
Anti-diarrhoeal.

CONTRAINDICATION

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.

WARNINGS AND PRECAUTIONS

The administration of Zedott Kid does not modify the usual rehydration regimens. It is essential for the child to drink abundant liquids.

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.

In patients with diabetes, it should be taken into account that each sachet contains 2.899 g of sucrose.

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.

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.

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.

DRUG INTERACTION

To date, no interactions with other medicinal products have been described in humans.
In humans, joint treatment with racecadotril and loperamide or nifuroxazide does not modify the kinetics of racecadotril.

ADVERSE EFECTS

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 (≥ 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.

OVERDOSAGE

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.

DOSAGES AND ADMINISTRATION

Zedott Kid is administered via the oral route, together with oral rehydration.

Zedott Kid 30 mg 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 13 kg to 27 kg : one 30 mg sachet 3 times daily.

In children of more than 27 kg : two 30 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. Long-term treatment with racecadotril is not recommended.

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

Special populations:

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

USE IN PREGNANCY, NURSING MOTHER, AND SPECIAL 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 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, Zedott kid should not be administered to pregnant women.

Lactation:

Due to the lack of information regarding racecadotril secretion in human milk, this medicinal product should not be administered to breastfeeding women.

EXPIRY DATE

Do not use later than the date of expiry.

STORAGE

Store at a Temperature Not Exceeding 30°C, Protected From Light And Moisture

PRESENTATION

Zedott Kid is available as 3gm Sachet

MARKETED BY

TORRENT PHARMACEUTICALS LTD.
Torrent House, Off Ashram Road,
Ahmedabad-380 009, INDIA

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