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

Zedott (Racecadotril Capsules 100 mg)

COMPOSITION

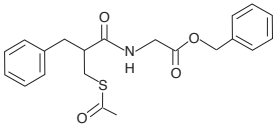
Each hard gelatin capsule contains :

Racecadotril Ph. Eur.	100 mg
Excipients	q.s.

Approved colours used in hard gelatin capsule shell

DESCRIPTION

Racecadotril Benzyl [[(2RS)-2-[(acetylsulfanyl)methyl]-3-phenyl propanoyl]amino]acetate is a lipophilic derivative of Thiorphan. Its empirical formula is $C_{21}H_{23}NO_4S$, its molecular weight is 385.47. Racecadotril is white or almost white powder which is practically insoluble in water, freely soluble in methanol and in methylene chloride. It is a dipeptide with a single amide bond developed from research into the structure-activity relationships of the enkephalinase molecule.



CLINICAL PHARMACOLOGY

Mechanism of Action

In peripheral tissues, orally administered racecadotril is rapidly hydrolysed to the more potent enkephalinase inhibitor thiorphan. Within these tissues, membrane-bound enkephalinase enzymes degrade endogenous opioids (enkephalins). Inhibition of enkephalinase by thiorphan increases the availability of opioids, which activate delta (δ) opioids receptors in the gastrointestinal tract. This in turn leads to a reduction in cAMP mucosal levels, resulting in a reduction in the secretion of water and electrolytes into the intestinal lumen (i.e. an antisecretory mechanism in contrast to loperamide which slows gastrointestinal transit).

Pharmacokinetics

After oral administration, racecadotril is rapidly absorbed and quickly metabolized to its active metabolite thiorphan, which in turn mediates all further actions. The activity on plasmatic enkephalinase appears 30 min after the administration. The peak plasma concentration of thiorphan is reached 60 min after administration of a single oral dose of racecadotril. The biological half-life of enkephalinase activity is 3 h. The pharmacokinetic parameters of repeated doses of racecadotril are similar on days 1 and 7 as those observed for a single oral dose.

Special Populations

There is no data for use of racecadotril in hepatic or renal insufficiency patients.

Pregnancy/Lactation

Safety and efficacy of racecadotril in pregnant / lactating women has not been established.

CLINICAL EFFICACY, SAFETY AND TOLERABILITY

The anti-diarrheal activity of Racecadotril is significantly greater than that of placebo on all the efficacy criteria studied and in particular on the most important criterion, the stool output for the first 24 and 48 hours in children aged from 1 month to 4 years. Likewise, the activity of Racecadotril was significantly greater on the other signs associated with diarrhea, such as dehydration in infants. This antisecretory effect is an indication of the reduction of stool output leading to a reduction of the major risks linked to dehydration in children, even in moderate climates.

In children over 2 years, age below which antimotility agents such as loperamide are contraindicated, Racecadotril is as effective as loperamide to treat the diarrhea itself and more effective than loperamide to treat associated symptoms, as the lowest frequency of abdominal pain and vomiting caused fewer associated treatments with Racecadotril.

Furthermore, the low incidence of rebound constipation with Racecadotril, significantly less frequent than that observed with loperamide, confirms the total absence of intestinal transit reduction, demonstrated experimentally in animals and in clinical pharmacology, as well as in clinical trials in adults.

In addition, there is maintenance of the intestinal transit time prevent stasis in the distended intestinal lumen, and consequent bacterial proliferation in the small intestine. These is the major risks associated with morphinomimetics in children, thus the lack of effect on intestinal transit time - constitutes an advantage for Racecadotril.

In children under 2 years, in whom the blood-brain barrier is immature and any treatment with morphinomimetics is contraindicated because of the risk of depression of the central nervous system, Racecadotril constitutes a valuable symptomatic treatment for diarrhea as a supplement to the administration of an oral rehydration solution. During clinical trials, the most commonly reported undesirable effects are vomiting, fever and respiratory disorders, occurring in more than 1% of patients. No alterations of the central nervous system have been observed.

During post marketing pharmacovigilance, the overall most frequent Adverse Events were cutaneous and/or allergic: mainly rash, erythemous/papulous reaction, prurigo or urticaria, but also few cases of multiform erythema, erythema nodosum, and lip or tongue oedema, angioneurotic oedema.

INDICATIONS AND USAGE

Zedott is an oral enkephalinase inhibitor used in the treatment of acute diarrhoea.

CONTRAINDICATIONS

Zedott is contraindicated in patients with known hypersensitivity to the ingredients of the formulation.

ADVERSE REACTIONS

Central Nervous System

Dizziness, malaise, and headache have accompanied therapy of acute diarrhoea in a few patients.

Metabolic

Persistence of hypokalemia has been reported infrequently in children with severe watery diarrhoea.

Gastrointestinal

Gastrointestinal adverse effects have been minimal, the incidence often not exceeding that of placebo. Constipation during treatment has been infrequent when placebo effects are eliminated, and less frequent than reported with loperamide. Abdominal distension has not been more common with racecadotril than placebo in available studies. Vomiting has occurred in up to 50% of children treated with racecadotril, although a high incidence has also been seen with placebo. Correcting for placebo effects, the incidence of vomiting in children is low (less than 10%).

OVERDOSAGE

No information is available on overdosage with racecadotril. In case of accidental over dosage, symptomatic treatment should be given.

DOSAGE AND ADMINISTRATION

The recommended dose of racecadotril is one capsule immediately and one capsule three times a day up to 5 days or upto two normal stools are recorded. Treatment should not exceed 7 days.

DIRECTION FOR USE

Zedott should be taken as whole.

EXPIRY DATE

Do not use later than the date of expiry.

STORAGE

STORE PROTECTED FROM LIGHT AND MOISTURE, BELOW 25^{O}C

Keep out of reach of children

PRESENTATION

Zedott is available in blister strips of 10 Capsules.

torrent

Manufactured by :
TORRENT PHARMACEUTICALS LTD.
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Teh. Nalagarh, Dist. Solan (H.P.), INDIA.