SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DOTRIVEL 10 mg INFANTS, oral powder in sachet-dose

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Racecadotril ..... 10 mg
For one sachet-dose.
Excipient with known effect: each sachet contains 979.83 mg of sucrose.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral powder in sachet-dose
White powder.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

In addition to oral rehydration, this is a symptomatic treatment for acute diarrhea in infants. The importance of rehydration with oral rehydration solution or intravenously should be adjusted according to the severity of the diarrhea, the child's age, and any other relevant factors (associated illnesses, etc.).

4.2. Posology and method of administration

Oral route.
DOTRIVEL 10 mg is indicated for infants from one month of age and weighing less than 13 kg.

Posology

The usual daily dosage is established according to body weight on the basis of 1.5 mg/kg per dose, up to a maximum of three doses spread throughout the day.

In practice:

Number of sachet(s) by socket in function of weight body of infant:

- For A infant of less of 9 kg: 1 sachet, 3 times by day
- For A infant of 9 has 13 kg: 2 sachets, 3 times by day.

Method of administration

The powder can be poured either into the food, or into a glass of water or a baby bottle, stirring well and giving the entire mixture to swallow immediately.
On the first day: one dose immediately, then, depending on the time of the first dose, up to a maximum of three doses spread throughout the day, including the initial dose. Doses should preferably be taken at the beginning of the three main meals.
The following days: three doses spread throughout the day, preferably at the beginning of the three main meals.
The maximum daily dosage is three doses.
The treatment will be continued until the return of two consecutive formed bowel movements, without exceeding 7 days.

Populations particulars

No studies have been conducted in children under 3 months of age.

No studies have been conducted in children with hepatic or renal impairment (see section 4.4).

4.3. Contraindications

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

4.4. Special warnings and precautions for use

Treatment with DOTRIVEL is only an adjunct to oral rehydration and in no way replaces it. Rehydration must be systematic in infants/children with acute diarrhea to prevent or treat dehydration, and must be adjusted to compensate for fluid and electrolyte losses.

The treatment of acute diarrhea in children is based primarily on correcting water and electrolyte losses through the use of oral rehydration solutions and early refeeding, the methods of which depend on the child's age and the type of diet prior to the diarrhea.
In cases of severe or prolonged diarrhea, significant vomiting, or refusal to eat, intravenous rehydration should be considered.

The presence of blood or pus in the stool, accompanied by fever, may indicate invasive bacterial diarrhea or other underlying illnesses. In cases of infectious diarrhea with clinical manifestations suggesting an invasive process, use antibacterial agents with good systemic penetration.

Racecadotril has not been evaluated in the treatment of antibiotic-associated diarrhea. Therefore, racecadotril should not be used in these cases.
Due to potentially reduced bioavailability, racecadotril should not be administered in cases of prolonged or uncontrollable vomiting.
Renal and hepatic insufficiency:
In cases of renal or hepatic insufficiency, DOTRIVEL should not be administered due to a lack of data.
Excipients:
This medicine contains sucrose. Patients with fructose intolerance, glucose-galactose malabsorption syndrome, or sucrase- isomaltase deficiency (rare hereditary disorders) should not take this medicine.
This medicine contains 0.97983 g of sucrose per sachet. If the amount of sucrose (a source of glucose and fructose) in the daily dose of this medicine exceeds 5 g per day, this should be taken into account in the daily intake for those on a low-sugar diet or with diabetes.
Hypersensitivities:
Skin reactions have been reported with the use of this medication. In most cases, these reactions are mild and do not require treatment. However, in some situations, these reactions can be severe and life-threatening; a link with racecadotril cannot be completely ruled out. If severe skin reactions occur, treatment with racecadotril should be stopped immediately.
Cases of hypersensitivity and angioedema have been reported in patients treated with racecadotril. These events can occur at any time during treatment.
Angioedema of the face, extremities, lips, and mucous membranes may occur .
When angioedema is associated with obstruction of the upper airways, such as at the level of the tongue, glottis and/or larynx, emergency treatment must be administered immediately.
Racecadotril should be discontinued and the patient should be closely monitored with appropriate follow-up until complete and sustained resolution of symptoms. Racecadotril should not be restarted.
Bradykinin-mediated angioedema :
Racecadotril or certain therapeutic classes are likely to cause a vascular reaction such as angioedema of the face and neck, resulting from the inhibition of bradykinin degradation.
The consequences of angioedema can sometimes be fatal, due to airway obstruction. Angioedema can occur independently of the simultaneous use of these medications, in cases where the patient has been previously exposed to one of the two drugs. A history of this effect should be sought, and the necessity of this type of combination should be assessed.
Combining racecadotril with certain drugs that increase bradykinin concentration, particularly angiotensin-converting enzyme (ACE) inhibitors (e.g., perindopril and ramipril), increases the risk of causing bradykinin-induced angioedema (see section 4.5).
Therefore, a rigorous benefit/risk assessment is necessary before initiating treatment with racecadotril in patients on ACE inhibitors (see section 4.5).

Serious cutaneous adverse reactions (SCAR):

Serious cutaneous adverse reactions (SCAR), including drug hypersensitivity syndromes with eosinophilia and systemic symptoms (DRESS) that may endanger life or be fatal, have been reported with racecadotril treatment. Patients must be informed of the signs and symptoms and close monitoring must be performed to detect possible skin reactions. In the event of the appearance of signs and symptoms suggestive of DRESS, racecadotril must be stopped immediately and an alternative treatment considered. If DRESS appears in a patient during racecadotril administration, racecadotril must under no circumstances be resumed in that patient.

4.5. Interactions with other medicinal products and other forms of interaction

Association not recommended :
Bradykinin drugs and angioedema

Certain drugs or therapeutic classes can cause angioedema-like vascular reactions of the face and neck, resulting from the inhibition of bradykinin degradation. The most frequently implicated drugs are ACE inhibitors (e.g., perindopril , ramipril), and to a lesser extent angiotensin II receptor antagonists (e.g., candesartan , irbesartan), mTOR inhibitors , gliptin -class antidiabetic drugs , racecadotril, estramustine , sacubitril , and recombinant altepase .
The consequences of angioedema can sometimes be fatal, due to airway obstruction. Angioedema can occur independently of the simultaneous use of these medications, in cases where the patient has been previously exposed to one of the two drugs. A history of this effect should be sought, and the necessity of this type of combination should be assessed.

Association not recommended (see also section 4.4)
+ Other drugs with a risk of bradykinin- induced angioedema (see section **Drugs, bradykinin and angioedema**)

Others
There socket concomitant of racecadotril with THE loperamide Or THE nifuroxazide born amended not there kine tic racecadotril .

4.6. Pregnancy and breastfeeding

Pregnancy
Animal studies have shown no direct or indirect harmful effects with respect to reproductive toxicity. Clinical data on the use of racecadotril during pregnancy are very limited. Consequently, as a precautionary measure, it is preferable to avoid the use of DOTRIVEL during pregnancy at any stage.

Breastfeeding
In the absence of data on the passage of racecadotril into milk and due to its pharmacological properties and the immaturity of the newborn's digestive tract, it should not be administered during breastfeeding.

Fertility
No effect on fertility was observed in fertility studies conducted in male and female rats.

4.7. Effects on the ability to drive vehicles and use machinery

Racecadotril has no or negligible effect on the ability to drive vehicles and use machines.

4.8. Undesirable effects

Clinical trials conducted during acute diarrhea provided safety data in 860 infants and children treated with racecadotril and 441 treated with placebo.
The adverse reactions listed below were observed more frequently with racecadotril than with placebo during clinical trials, or have been reported during the post-marketing period.
MedDRA system organ classes . Within each system organ class, adverse reactions are presented by frequency. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. The frequency of adverse reactions has been defined according to 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).
Severe adverse skin reactions (SCARs), including hypersensitivity syndromes medicinal with eosinophilia And symptoms systemic (DRESS) have adverse events have been reported with treatment with racecadotril (see Section 4.4).

Organ system classes	**Frequency**	**Undesirable effect**
Skin and subcutaneous tissue disorders (see section 4.4)	Uncommon	Rash, erythema.
	Frequency not known	Urticaria, angioedema , edema of the tongue, face, lip, eyelid, erythema multiforme, erythema nodosum, papular rash , pruritus, prurigo, drug reaction with eosinophilia and systemic symptoms (DRESS)
Immune system disorder	Frequency not known	Anaphylactic shock

Reporting suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals report any adverse effects

suspected unwanted substance via the FRILAB declaration form available under the tab Pharmacovigilance information from the website: www.frilab.ch

4.9. Overdose

In the reported cases of overdose, patients did not experience any adverse effects.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic class : OTHER ANTIDIARRHEAL (INTESTINAL ANTISECRETORY MEDICINE.
ATC code: A07XA04. (HAS: device digestive And metabolism).
Racecadotril is a prodrug that must be hydrolyzed into its active metabolite, thiorphan, which is an inhibitor of enkephalinase , a cell membrane enzyme present in various tissues, including the intestinal epithelium.

This enzyme contributes to the hydrolysis of exogenous and endogenous peptides, such as enkephalins. Racecadotril thus protects enkephalins from enzymatic degradation, prolonging their action at the enkephalinergic synapses of the small intestine and thereby reducing hypersecretion. Racecadotril is a pure intestinal antisecretory agent. It decreases intestinal hypersecretion of water and electrolytes induced by cholera toxin or inflammation, without affecting basal secretion. It exerts antidiarrheal activity without altering intestinal transit time. In two clinical studies conducted in children, racecadotril reduced stool weights by 40% and 46%, respectively, within the first 48 hours. A significant reduction in the duration of diarrhea and the need for rehydration was also observed. A meta-analysis (9 randomized clinical trials, racecadotril versus placebo, in addition to oral rehydration solution) collected individual patient data from 1,384 boys and girls with acute diarrhea of varying severity, treated as outpatients or inpatients. The mean age was 12 months (interquartile range: 6 to 39 months). A total of 714 patients were under 1 year old and 670 patients were over 1 year old. The mean weight ranged from 7.4 kg to 12.2 kg across the studies. The mean overall duration of diarrhea after enrollment was 2.81 days in the placebo group and 1.75 days for racecadotril. When administered orally, racecadotril's activity remains peripheral, with no effect on the central nervous system. A randomized, crossover clinical study showed that racecadotril 100 mg at the therapeutic dose (1 capsule) or at a higher dose (4 capsules) does not induce QT/ QTc prolongation in 56 healthy adult volunteers (unlike the effect observed with moxifloxacin , used as a positive control).

5.2. Pharmacokinetic properties

Absorption
After oral administration, racecadotril is rapidly absorbed. Activity on plasma enkephalinase appears as early as thirty minutes.
The bioavailability of racecadotril is not affected by food, but the peak activity is delayed by about 1.5 hours.

Distribution
Following oral administration of 14C-labeled racecadotril to healthy volunteers, the concentration of racecadotril was approximately 200 times higher in plasma than in blood cells and approximately 3 times higher in plasma than in total blood volume. Racecadotril does not bind significantly to blood cells.
In plasma, the mean apparent volume of distribution of 66.4 L/kg demonstrates a moderate distribution of 14C in other tissues.
Ninety percent of the active metabolite of racecadotril, tiorphan , (RS)-N-(1-oxo-2-(mercaptomethyl) -3- phenylpropyl)glycine, is bound to plasma proteins, primarily albumin. The pharmacokinetic properties of racecadotril are not altered by repeated dosing or in elderly patients.
The magnitude and duration of action of racecadotril are dose-dependent. The peak concentration is reached at approximately 2.5 hours and corresponds to a 90% inhibition of enzyme activity at the administered dose of 1.5 mg/kg. For a dose of 100 mg, the duration of activity on plasma enkephalinase is approximately 8 hours.

Biotransformation
The biological half-life of racecadotril, determined from plasma inhibition of enkephalinase , is 3 hours.
Racecadotril is rapidly hydrolyzed to tiorphan (RS)-N-(1-oxo-2-(mercaptomethyl) -3-phenylpropyl)glycine, its active metabolite, which is itself transformed into the inactive metabolite S- methylthiorphan sulfoxide , S methyl tiorfan , 2-methanesulfinylmethylpropionic acid and 2-methylsulfanylmethylpropionic acid, which were all formed at more than 10% of systemic exposure to the parent molecule.

Other minor metabolites have also been detected and quantified in urine and feces. Repeated administration of racecadotril does not lead to accumulation in the body.
In vitro data show that racecadotril/ thiorfan and its four major inactive metabolites do not act significantly as inhibitors of cytochrome isoforms CYP 3A4, 2D6, 2C9, 1A2 and 2C19.

In vitro data show that racecadotril/ thiorfan and its four major inactive metabolites do not act significantly as inducers of cytochrome CYP isoforms (family 3A, 2A6, 2B6, 2C9/2C19, family 1A, 2E1) and enzymes that bind to glucuronyltransferase .
Racecadotril does not alter the protein binding of highly protein-bound products, such as tolbutamide, warfarin, niflumic acid , digoxin , or phenytoin .
In patients with liver failure (cirrhosis, Child -Pugh B), the kinetic profile of the metabolite shows the same Tmax and T1 /2 , and lower Cmax (-65%) and Area under the curve (-29%), compared to healthy subjects.

In patients with severe renal impairment (creatinine clearance between 11 and 39 ml/min), the kinetic profile of the metabolite shows a lower Cmax (-49%) and larger Area under the Curve (+15%) and T 1/2 , compared to healthy volunteers (creatinine clearance > 70 ml/min).

In the pediatric population, pharmacodynamic results are similar to those in the adult population, with Cmax reached 2 hours and 30 minutes after administration. There is no accumulation after administration of repeated doses every 8 hours for 7 days.

Elimination
Racecadotril is eliminated via its active and inactive metabolites. Elimination occurs primarily via the kidneys (81.4%), and to a lesser extent via the feces (approximately 8%). Pulmonary excretion is negligible (less than 1% of the dose).

5.3. Preclinical safety data

Four-week chronic toxicity studies in monkeys and dogs, useful for assessing the duration of treatment in humans, showed no effect at dosages up to 1250 mg/kg/day and 200 mg/kg, which correspond to safety margins of 625 and 62 (relative to humans) respectively.

Racecadotril was not found to be immunotoxic in mice treated for 1 month.
Longer-term exposure (1 year) in monkeys showed widespread infections and reduced antibody responses to vaccination (at a dose of 500 mg/kg/day) and no infection/immune depression at 120 mg/kg/day.
Similarly, in dogs treated with a dose of 200 mg/kg/day for 26 weeks, some infectious/immune reactions were detected. Their clinical significance is unknown: refer to section 4.8

mutagenic or clastogenic effects of racecadotril were detected in standard in vivo and in vitro tests. Carcinogenicity tests were not performed as this is a short-term treatment.
Reproductive and developmental toxicity studies (pre-embryonic development and fertility, prenatal and postnatal development, embryo- fetal development studies) have not revealed any particular effects of racecadotril.
Others effects preclinical (such as severe anemia presumably aplastic, increase in there diuresis , ketonuria, diarrhea) have summer observed only during of a has exposure enough superior by report at the exhibition maximum at the house of the man. Their meaning clinical is not not known.

A toxicity study in juvenile rats showed no significant effects from racecadotril at doses up to 160mg/kg/day, which corresponds to a dose 35 times higher than the recommended pediatric dose (e.g., 4.5mg/kg/day).
Despite the immaturity of renal function in children under 1 year of age, higher levels of exposure are not expected in them.

Other safety pharmacology studies have not shown any adverse effects on the central nervous system, the cardiovascular system, or respiratory functions.
In animals, racecadotril enhances the effect of butylhyoscine on intestinal transit and on the anticonvulsant effect of phenytoin .

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sucrose, colloidal silicon dioxide, polyvinyl pyrrolidone.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

Store at a temperature below 30°C.

6.5. Nature and contents of container

1 g of powder in sachet-dose (LDPE/Aluminium/LDPE/Paper), box of 10

6.6. Special precautions for disposal and handling

No special requirements for disposal.

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

7. OPERATOR

FRILAB SA
17, rue des Pierres du Niton
1207 Geneva
SWISS

8. MANUFACTURER

Athena Drug Delivery Solutions Pvt. Ltd.
A-1 to A-5, MIDC, Chemical Zone,
Ambernath (W), District Thane-421501

9. DATE OF REVISION OF THE TEXT

October 2024

10. DOSIMETRY

Not applicable

CONDITIONS FOR PRESCRIPTION AND DISPENSING

List I