SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

TIORFAN 10 mg, capsule

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Racecadotril.....100 mg.
For one capsule.

Excipient with known effect: Each capsule contains 41 mg of monohydrated lactose.
For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Capsule
Capsule of ivory colour, size 2, containing a white powder with a smell of sulphur.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

TIORFAN is indicated in the symptomatic treatment of acute diarrhoea in adults, as a supplement to dietary measures.

4.2. Posology and method of administration

Oral administration.
Medication reserved for adults.
Adult:
One capsule to start, at whatever time, then one capsule three times per day, for preference at the beginning of the three main meals.
The treatment is continued until two solid stools are obtained. Never exceed 7 days of treatment.
Particular populations:
Paediatric population:
Tiorfan 100 mg capsule must not be used among infants or children.
There are other pharmaceutical forms of TIORFAN adapted for administration in the paediatric population.
Elderly population:
There does not seem to be any justification for posology adjustment with elderly patients (see Section 5.2)

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

The administration of TIORFAN does not dispense with a rehydration process if necessary.
In the presence of signs of an acute dysenteric syndrome, such as the presence of blood in the stool or a fever, Racecadotril must not be used.
Racecadotril has not been evaluated, and must not be used, in the course of diarrhoea associated with antibiotics.
There is not sufficient data relating to chronic diarrhoea in connection with this medicinal product.

This information is confidential

Data is limited with regard to patients with hepatic or renal insufficiency. These patients must therefore be treated with prudence (see Section 5.2).

The bioavailability may be reduced among patients with prolonged vomiting.

This medicinal product contains lactose. Its use is not recommended among patients presenting galactose intolerance, Lapp lactose deficit, or a glucose or galactose malabsorption syndrome (rare hereditary disorders).

Cutaneous reactions have been reported with the use of this medicinal product. In the majority of cases, these reactions are slight and do not require any treatment. In certain situations, however, these reactions can be severe and potentially life-threatening; a link with the taking of Racecadotril cannot be entirely excluded. If severe cutaneous reactions do appear, treatment by Racecadotril must be terminated immediately.

Cases of hypersensitivity and Quincke's oedema have been reported among patients treated with Racecadotril. These events may occur at any time in the course of the treatment. An angioedema of the face, extremities, lips, and the mucous membranes may be incurred.

If the angioedema is associated with an obstruction of the upper respiratory passages, for example in the region of the tongue, the glottis, and/or of the larynx, emergency treatment should be administered rapidly.

Racecadotril must be interrupted and the patient put under close medical supervision, with initiation of appropriate follow-up until the complete and permanent disappearance of the symptoms.

Patients with antecedents of angioedema not associated with treatment by Racecadotril may present an enhanced risk of developing angioedema.

The concomitant use of Racecadotril and enzyme conversion inhibitors (ECI) can augment the risk of Quincke's oedema (see section 4.5). In consequence, a rigorous evaluation of the benefit/risk ratio is necessary before initiating treatment with Racecadotril among patients under treatment with enzyme conversion inhibitors.

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

Interaction of Racecadotril with enzyme conversion inhibitors (ECI).

The concomitant use of Racecadotril and **enzyme conversion inhibitors (ECI,** such as, for example, captopril, enalapril, lisinopril, perindopril, ramipril) can augment the risk of Quincke's oedema (see section 4.4).

The concomitant administration of Racecadotril with loperamide or nifuroxazide does not modify the kinetics of Racecadotril.

4.6. Fertility, pregnancy, and lactation

Fertility

No effect on fertility has been observed during fertility studies conducted among male and female rats.

Pregnancy

Animal studies have not revealed any direct or indirect harmful effect with regard to toxicity affecting reproduction. Clinical data on the use of Racecadotril in the course of pregnancy is very limited. In consequence, it is preferable as a matter of prudence to avoid the use of TIORFAN in the course of pregnancy, at whatever term.

Breast-feeding

In the absence of data regarding the passing of Racecadotril into mother's milk, and due to its pharmacological properties and the immaturity of the digestive tract of the neonate, TIORFAN should not be administered in the course of breast-feeding.

4.7. Effects on ability to drive and use machines

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

4.8. Undesirable effects

Within the framework of clinical tests relating to acute diarrhoea, data is available regarding 2193 adults treated with Racecadotril and 282 treated with placebo.

The undesirable effects listed below have been observed by organ system class more frequently with Racecadotril than with placebo in the course of clinical tests, or have been reported during the marketing period.

The frequency of undesirable effects has been defined by organ class and in accordance with the following convention: Very common (>1/10), common (>1/100 to <1/10), uncommon (>1/1000 to <1/100), rare (>1/10000 to < 1/1000), very rare {<1/10000), not known (cannot be estimated on the basis of the data available).

Disorders of the nervous central nervous system

This information is confidential

Frequent: Headache

Disorders of the skin and subcutaneous tissue

Uncommon: Rash, erythema

Frequency not known: Polymorphous erythema, oedema of the tongue, the face, lips or eyelids, angio-oedema (Quincke's oedema), urticaria, erythema nodosum, papular rash, pruritus, prurigo, toxidermia.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system: National Agency for Medicines and Health Products Safety (ANSM) and the network of Regional Pharmacovigilance Centres - Internet site: www.ansm.sante.fr.

4.9. Overdose

In the cases of overdose reported, the patients did not present any undesirable effects.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic class: OTHER ANTIDIARRHETIC (MEDICATION FOR ANTI-INTESTINAL SECRETION. Code ATC: A07XA04. (A: Digestive system and metabolism).

Racecadotril is a prodrug which must be hydrolysed into its active metabolite, tiorfan, which is an inhibitor of enkephalinase, an enzyme of the cellular membrane, present in different tissues, among them the intestinal epithelium.

This enzyme contributes to the hydrolysis of exogenic and endogenic peptides, such as the enkephalins.

Racecadotril accordingly protects the enkephalins against enzymatic degradation, thereby prolonging their action at the level of the enkephalinergic synapses of the small intestine, thereby reducing hypersecretion.

Racecadotril is a pure anti-intestinal secretion substance. It reduces the intestinal hypersecretion of water and electrolytes induced by cholera toxin or inflammation, without having any effect on basal secretion. It exercises a rapid antidiarrhetic effect, without change to intestinal transit time.

Racecadotril does not incur any abdominal inflation. During clinical tests, secondary constipation is observed with the same frequency in the Racecadotril and placebo groups.

By oral administration, the activity is solely peripheral, without any effect on the central nervous system.

A randomised and crossed clinical study has shown that Racecadotril 100 mg in the therapeutic dose (1 capsule) or in a higher dose (4 capsules) did not induce any prolongation of the QT/QTc among 56 healthy adult volunteers (contrary to the effect observed with moxifloxacine, used as a positive control).

5.2. Pharmacokinetic properties

Absorption:

After oral administration, Racecadotril is absorbed rapidly. The activity on the plasma enkephalinase appears after the thirtieth minute.

The bioavailability of Racecadotril is not changed by food, but the activity peak is delayed by about one and a half hours.

Distribution:

After oral administration of Racecadotril marked with ^{14}C among healthy volunteers, the concentration of Racecadotril was about 200 times greater in the plasma than in the blood cells, and about 3 times greater than in the total blood volume. Racecadotril does not bond to blood cells in any significant manner.

In the plasma, the apparent mean distribution volume of 66.4 L/kg demonstrates a moderate distribution of ^{14}C in the other tissues.

90% of the active metabolite of Racecadotril, tiorfan, (RS)-N-(1-oxo-2-(mercaptomethyl)-3- phenylpropyl) glycine, bonds to the plasma proteins, principally albumin.

The pharmacokinetic properties of Racecadotril are not changed during the administration of repeated doses or in elderly subjects.

The amplitude and duration of action of Racecadotril are associated with the dose administered. The peak of concentration on plasma enkephalinase occurs about 2 hours after administration, and corresponds to an inhibition of 75 % for the dose of 100 mg.

For a dose of 100 mg, the duration of activity on the plasma enkephalinase is about 8 hours.

Metabolism:

This information is confidential

The biological half-life of Racecadotril, determined on the basis of the plasma inhibition of enkephalinase, is 3 hours.

Racecadotril is rapidly hydrolysed into tiorfan (RS)-N-(1-oxo-2-(mercaptomethyl)-3-phenylpropyl) glycine, its active metabolite, which itself transforms into inactive metabolites S-methyltiorfan sulfoxide, S methyl tiorfan,

2- methanesulfinylmethyl propionic acid and 2-methylsulfanylmethyl propionic acid, which are all formed at more than 10% of the systemic exposure of the mother molecule.

Other minor metabolites have likewise been detected and quantified in the urine and faecal matter.

The repeated administration of Racecadotril does not induce accumulation in the organism.

The *in vitro* data shows that Racecadotril/tiorfan and its four major inactive metabolites do not act in a significant manner as inhibitors of isoforms of the cytochrome CYP 3A4, 2D6, 2C9, 1A2 and 2C19.

The *in vitro* data shows that Racecadotril/tiorfan and its four major inactive metabolites do not act in a significant manner as inductors of isoforms of the cytochrome CYP (family 3A, 2A6, 2B6, 2C9/2C19, family 1A, 2E1) and the enzymes which bond to glucuronyltransferase.

Racecadotril does not change the protein bond of products which are strongly bonded to proteins, such as tolbutamide, warfarin, niflumic acid, digoxin or phenytoin.

Among patients with hepatic insufficiency (cirrhosis, Child-Pugh B), the kinetic profile of the metabolite demonstrates the same T max and $T^{1/2}$, and lower C max (-65 %) and area beneath the curve (-29 %), in relation to healthy subjects.

Among patients with severe renal insufficiency (creatinine clearance between 11 and 39 ml/min), the kinetic profile of the metabolite demonstrates a lower C max (-49 %) and larger area under the curve (+15 %) and $T^{1/2}$, in relation to healthy volunteers (creatinine clearance > 70 ml/min).

In the paediatric population, the pharmacodynamic properties are similar to those of the adult population, with a C max attained at 2 hours 30 minutes after the administration. There is no accumulation after administration of repeated doses every 8 hours, for 7 days.

Excretion:

Racecadotril is eliminated by way of its active and inactive metabolites. The elimination is effected in particular by the renal route (81.4%), and to a lesser degree in the faeces (about 8%). Excretion by the pulmonary route is not significant (less than 1% of the dose).

5.3. Preclinical safety data

Studies of chronic toxicity of 4 weeks carried out with apes and dogs, used of the evaluation of the duration of treatment among humans, does not provide evidence of any effect at dosages of up to 1250 mg/kg/day and 200 mg/kg which corresponds to safety margins of 625 and 62 (in relation to humans) respectively.

Racecadotril has not been found to be immunotoxic to mice for 1 month.

An exposure of longer duration (one year) in apes demonstrated generalised infections and reduced responses to antibodies on vaccination (at a dose of 500 mg/kg/day) and no infection/immune depression at 120 mg/kg/day.

Likewise, in dogs treated at a dose of 200 mg/kg/day for 26 weeks, a number of infectious/immune reactions were detected. The clinical significance is little understood; refer to section 4.8.

No mutagenic or clastogenic effect of Racecadotril was detected during standard tests *in vivo* and *in vitro.*

No tests of carcinogenicity have been carried out, since only short duration treatment is involved.

Studies of reproductive and development toxicity (pre-embryonic and fertility development, pre-natal and post-natal development, studies of embryo-foetal development) have not revealed any particular effect of Racecadotril.

Other preclinical effects (such as severe anaemia, probably aplasic, increase of diuresis, ketonuria, diarrhoea) were observed only after exposure sufficiently greater in relation to the maximum exposure for humans. Their clinical significance is not known.

A toxicity study conducted among juvenile rats did not provide any evidence of a significant effect due to Racecadotril at doses up to 160mg/kg/day, which corresponds to a dose 35 times higher than the recommended paediatric dose (e.g. 4.5 mg/kg/day).

Despite the immaturity of the renal function among children of less than 1 year old, higher levels of exposure are not anticipated among them.

Other pharmacology safety studies have not shown any evidence of harmful effect on the central nervous system, the cardiovascular system, or the respiratory functions.

Among animals, Racecadotril reinforces the effect of butylhyoscine on the intestinal tract or on the anticonvulsant effect of phenytoin.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

This information is confidential

Monohydrated lactose, pregelatinised maize starch, magnesium stearate, anhydrous colloidal silica.
Composition of the capsule envelope: Gelatin, titanium dioxide (E171), yellow iron oxide (E172).

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years

6.4. Special precautions for storage

This medicinal product does not require any special precautions for storage.

6.5. Nature and contents of container

20 capsules under film (PVC-PVDC/Aluminium)

6.6. Special precautions for disposal and other handling

No special requirements.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

BIOPROJET PHARMA
9 RUE RAMEAU
75002 PARIS

Manufacturer

Laboratoires Sophartex

23 Rue du Pressoir, 28500, Vernouillet, France

8. MARKETING AUTHORISATION NUMBER(S)

07544/07363/VAR/2020

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Jul 16, 2022

10. DATE OF REVISION OF THE TEXT

[To be completed subsequently by the holder]

11. DOSIMETRY

Not applicable.

12. INSTRUCTIONS FOR THE PREPARATION OF RADIOPHARMACEUTICALS

This information is confidential