USE OF 4-CYCLOPROPYLMETHOXY-*N*-(3,5-DICHLORO-1-OXIDO-4-PYRIDIN-4-YL)-5-(METHOXY)PYRIDINE-2-CARBOXAMIDE FOR THE TREATMENT OF CRANIAL TRAUMAS

The present invention relates to the use of 4-cyclopropylmethoxy-*N*-(3,5-dichloro-1-oxidopyridin-4-yl)-5-(methoxy)pyridine-2-carboxamide, in the form of a hydrate, of a solvate, of a base or of an addition salt with an acid, for the preparation of a medicament for use in the treatment of cerebral traumas.

4-Cyclopropylmethoxy-*N*-(3,5-dichloro-1-oxidopyridin-4-yl)-5-(methoxy)pyridine-2-carboxamide, or alternatively called *N*-(3,5-dichloro-1-oxido-4-pyridinio)-4-cyclopropylmethoxy-5-methoxypyridine-2-carboxamide, is known to be part of the composition of medicaments for use in the treatment of various pathologies, including in particular inflammations of the joints, arthritis and rheumatoid arthritis. This compound, in hemihydrate form, is described, for example, in document WO95/04045 (compound referenced FR).

There exists a need to find medicaments for treating patients suffering from cerebral traumas. Studies have shown, in animals, that a possible approach is the administration of compounds which inhibit phosphodiesterases 4 (PDE 4), such as, for example rolipram. However, clinical studies have shown that this compound, and also other inhibitors of PDE 4, induce emetic effects which do not allow it to be used in therapy.

It has now been found that 4-cyclopropylmethoxy-*N*-(3,5-dichloro-1-oxidopyridin-4-yl)-5-(methoxy)pyridine-2-carboxamide can be used in the treatment of cerebral traumas, while at the same time avoiding the emetic effects at therapeutically acceptable doses.

A first subject of the invention therefore relates to the use of 4-cyclopropylmethoxy-*N*-(3,5-dichloro-1-oxidopyridin-4-yl)-5-(methoxy)pyridine-2-carboxamide for the preparation of a medicament for use in the treatment of cerebral traumas.

According to one embodiment of the invention, the use of 4-cyclopropylmethoxy-*N*-(3,5-dichloro-1-oxidopyridin-4-yl)-5-(methoxy)pyridine-2-carboxamide can be carried out with the latter in the form of a base or of an addition salt with an acid.

The salts that can be used in the context of the invention can be prepared with

pharmaceutically acceptable acids, but the salts of other acids that are useful, for example, for the purification or the isolation of 4-cyclopropylmethoxy-*N*-(3,5-dichloro-1-oxidopyridin-4-yl)-5-(methoxy)pyridine-2-carboxamide are also part of the invention.

The use of 4-cyclopropylmethoxy-*N*-(3,5-dichloro-1-oxidopyridin-4-yl)-5-(methoxy)-pyridine-2-carboxamide according to the invention can also be carried out with the latter in the form of a hydrate or of a solvate. The term "hydrate or solvate" is intended to mean the association or the combination of one or more molecules of 4-cyclopropyl-methoxy-*N*-(3,5-dichloro-1-oxidopyridin-4-yl)-5-(methoxy)pyridine-2-carboxamide with one or more molecules of water or of solvent.

For the purpose of the present invention, the term "cerebral traumas" is intended to mean traumas of external origin, such as, for example, cranial traumas caused in particular by an impact, a road accident, a fall or crushing.

A second subject of the invention relates to a pharmaceutical composition comprising 4-cyclopropylmethoxy-*N*-(3,5-dichloro-1-oxidopyridin-4-yl)-5-(methoxy)pyridine-2-carboxamide as active ingredient, and one or more pharmaceutically acceptable excipients.

The composition used according to the invention comprises an effective dose of the active ingredient.

For example, the daily doses of active ingredient that can be used according to the invention are from 0.001 to 10 mg/day.

According to the usual practice, the dosage appropriate for each patient is determined by the physician according to the method of administration and the age, weight and response of said patient.

The doses depend on the desired effect, on the duration of treatment and on the route of administration used.

There may be specific cases where higher or lower dosages are appropriate. Such dosages do not depart from the context of the invention.

The excipients are chosen, according to the pharmaceutical form and the method of

administration desired, from the usual excipients which are known to those skilled in the art.

The composition may be administered orally, parenterally or rectally.

The appropriate unit administration forms comprise oral administration forms, such as tablets, soft or hard gel capsules, powders, granules and oral solutions or suspensions, sublingual, buccal, intratracheal, intraocular and intranasal administration forms, forms for administration by inhalation, topical, transdermal, subcutaneous, intramuscular, intravenous or intrathecal administration forms, rectal administration forms, and implants. For topical application, the active ingredients according to the invention may be used in creams, gels, ointments or lotions.

When a composition is prepared in tablet form, the active ingredient is mixed with one or more pharmaceutical excipients, such as gelatin, starch, lactose, magnesium stearate, talc, silica, gum arabic, mannitol, microcrystalline cellulose, hypromellose or the like.
The tablets may be coated with sucrose, with a cellulosic derivative or with other substances suitable for coating. The tablets may be produced by various techniques, such as direct compression, dry or wet granulation, or hot melt.
It is also possible to obtain a pharmaceutical composition in the form of a gel capsule by mixing the active ingredient with a diluent and transferring the mixture obtained into soft or gel capsules.
For parenteral administration, use is made of aqueous suspensions, isotonic saline solutions or sterile injectable solutions which contain pharmacologically compatible agents, for example propylene glycol or butylene glycol.

By way of example, a unit administration form of 4-cyclopropylmethoxy-*N*-(3,5-dichloro-1-oxidopyridin-4-yl)-5-(methoxy)pyridine-2-carboxamide in tablet form comprises the following ingredients:

4-Cyclopropylmethoxy-*N*-(3,5-dichloro-1-oxidopyridin-4-yl)-5-(methoxy)pyridine-2-carboxamide	1 mg
Mannitol	224 mg
Sodium croscarmellose	5 mg
Maize starch	15 mg
Hydroxypropylmethylcellulose	2 mg

Magnesium stearate	3 mg

The effects of 4-cyclopropylmethoxy-*N*-(3,5-dichloro-1-oxidopyridin-4-yl)-5-(methoxy)-pyridine-2-carboxamide used according to the invention were evaluated in a cranial trauma model.

Experiment 1: Effect of chronic treatment with the compound of the invention in the CFR (Conditioned Freezing Response) test after a parietal cranial trauma

After general anaesthesia, rats (Sprague-Dawley, male, 150-200 g, Charles River) are placed in a stereotaxis frame. A craniotomy is performed at the level of the parietal cortex (AP: 3.5 mm; LAT: 7 mm and 3.5 mm below the cranial roof). A catheter connected to an HPLC pump is placed in contact with the dura mater and a pressure of 0.073 Kpsi is exerted.

The animals are treated intravenously 4 h after the surgery (D0) by administering a solution of 4-cyclopropylmethoxy-*N*-(3,5-dichloro-1-oxidopyridin-4-yl)-5-(methoxy)-pyridine-2-carboxamide in the carrier (PEG200 / physiological saline (NaCl 0.9%)), at the dose of 0.05 mg/kg.

Starting from D1 and up to D21 post-surgery, the animals are treated with a solution containing 4-cyclopropylmethoxy-*N*-(3,5-dichloro-1-oxidopyridin-4-yl)-5-(methoxy)-pyridine-2-carboxamide in the carrier (methylcellulose (MC) (0.6%) + tween-80 (0.5%) in water) *per os,* twice a day, at the total daily dose of 0.1 mg/kg.

The deficiency in the CFR was measured at days D23 and D24 post-surgery.

At D23, the animal is placed in a box, where it receives an electric shock of 0.6 mA for 1.5 s.

At D24, the animal is again placed in the same box and the duration of immobility is measured for 3 minutes.

A lesion induced by a trauma of the parietal cortex significantly reduces the immobility time.

The treatment with 4-cyclopropylmethoxy-*N*-(3,5-dichloro-1-oxidopyridin-4-yl)-5-(methoxy)pyridine-2-carboxamide at the dose of 0.1 mg/kg/day produces 100% inhibition of the deficiency induced by a cranial trauma ($p < 0.001$ in comparison with the traumatized animal given the carrier).

Experiment 2: Evaluation of the emetic effects of 4-cyclopropylmethoxy-*N*-(3,5-dichloro-1-oxidopyridin-4-yl)-5-(methoxy)pyridine-2-carboxamide.

The emetic capacity of 4-cyclopropylmethoxy-*N*-(3,5-dichloro-1-oxidopyridin-4-yl)-5-(methoxy)pyiridine-2-carboxamide was evaluated in the ferret. Two groups of ferrets were used, the first receiving the carrier (PEG200) and the second receiving 4-cyclopropylmethoxy-*N*-(3,5-dichloro-1-oxidopyridin-4-yl)-5-(methoxy)pyridine-2-carboxamide in solution in the carrier (PEG 200), by oral gavage. The animals were observed continually for the 2 hours following the administration, and then every hour up to 6 hours after the administration. The clinical signs (in particular retching and vomiting) were noted.

When administered at 0.1 mg/kg, 4-cyclopropylmethoxy-*N*-(3,5-dichloro-1-oxidopyridin-4-yl)-5-(methoxy)pyridine-2-carboxamide induces no retching or vomiting in the 5 ferrets treated.

These results show that the administration of a therapeutic dose of 4-cyclopropylmethoxy-*N*-(3,5-dichloro-1-oxidopyridin-4-yl)-5-(methoxy)pyridine-2-carboxamide for treating cerebral traumas does not cause any emetic effect.

Example 3: Evaluation of the emetic effects of (*R*)-(-)rolipram (((4R)-4-[3-(cyclopentyloxy)-4-methoxyphenyl]pyrrolidine-2-one)).

The emetic capacity of (*R*)-(-)-rolipram was evaluated in the ferret. Two groups of ferrets were used, the first receiving the carrier (PEG200) and the second receiving 4-cyclopropylmethoxy-*N*-(3,5-dichloro-1-oxidopyridin-4-yl)-5-(methoxy)pyridine-2-carboxamide in solution in the carrier (PEG 200), by oral gavage, at doses of 0.05 mg/kg and of 0.1 mg/kg. The animals were observed continually for the 2 hours following the administration, and then every hour up to 6 hours after the administration. The clinical signs were noted.

When administered at 0.05 mg/kg and 0.1 mg/kg, (*R*)-(-)-rolipram induces vomiting in

the ferrets treated.

The results of example 3 show that the administration of a therapeutic dose of (*R*)-(-)-rolipram causes any emetic effects.

Thus, 4-cyclopropylmethoxy-*N*-(3,5-dichloro-1-oxidopyridin-4-yl)-5-(methoxy)pyridine-2-carboxamide is of use in the preparation of a medicament for the treatment of cerebral traumas, such as, for example, traumas occurring during a fall, an impact or a car accident, while at the same time avoiding possible emetic effects at acceptable therapeutic doses.

CLAIMS

1. Use of 4-cyclopropylmethoxy-*N*-(3,5-dichloro-1-oxidopyridin-4-yl)-5-(methoxy)pyridine-2-carboxamide, in the form of a hydrate, of a solvate, of a base or of an additional salt with an acid, for the preparation of a medicament for use in the treatment of cerebral traumas.

2. Use according to Claim 1, characterized in that the 4-cyclopropylmethoxy-*N*-(3,5-dichloro-1-oxidopyridin-4-yl)-5-(methoxy)pyridine-2-carboxamide is in the form of a base.