(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 December 2009 (10.12.2009)

PCT

(10) International Publication Number
WO 2009/147178 A2

(51) **International Patent Classification**:
A61K 31/4439 (2006.01) *A61P 7/10* (2006.01)

(21) **International Application Number**:
PCT/EP2009/056824

(22) **International Filing Date**:
3 June 2009 (03.06.2009)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:
08157528.4 4 June 2008 (04.06.2008) EP

(71) **Applicant** *(for all designated States except US)*: **NYCOMED GMBH** [DE/DE]; Byk-Gulden-Str. 2, 78467 Konstanz (DE).

(72) **Inventor; and**
(75) **Inventor/Applicant** *(for US only)*: **HEINZE, Hartmut** [DE/DE]; Scheffelstr. 19, 78476 Allensbach (DE).

(74) **Agents**: **WILD, Robert** et al.; c/o Nycomed GmbH, P.O. Box 100310, 78403 Konstanz (DE).

(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

WO 2009/147178 A2

(54) **Title**: NOVEL MEDICAL USE OF SUBSTITUTED PYRIDIN-2-YLMETHYLSULPHINYL-1H-BENZIMIDAZOLES

(57) **Abstract**: The invention is directed to a new use of substituted pyridyl-2-methylsulfinylbenzinnidazoles for a treatment and/or prophylaxis of brain edema.

Novel medical use of substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazoles

Field of application of the invention

The invention relates to the use of substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazoles, i.e. proton pump inhibitors, and here especially pantoprazole for the treatment and / or prophylaxis of brain edema.

Known technical background

Pyridin-2-ylmethylsulphinyl-1H-benzimidazoles are well known for their H^+/K^+-ATPase-inhibitory action. These compounds are, owing to their mechanism of action, also referred to as proton pump inhibitors or, abbreviated, as PPI. Such sulfinyl derivates are described in a variety of patents and patent applications and here especially EP-A-0005129, EP-A-0166287, EP-A-0174726, EP-A-0254588 and EP-A-0268956 should be mentioned. Compounds as described in these later mentioned patents are of considerable importance in the therapy of disorders associated with an increased secretion of gastric acid.

Examples of active compounds from this group which are commercially available or in clinical development are 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulphinyl]-1H-benzimidazole (INN: omeprazole), (S)-5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulphinyl]-1H-benzimidazole (INN: esomeprazole), 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole (INN: pantoprazole), 2-[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)methylsulphinyl]-1H-benzimidazole (INN: lansoprazole), 2-{[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]methylsulphinyl}-1H-benzimidazole (INN: rabeprazole) and 5-methoxy-2-((4-methoxy-3,5-dimethyl-2-pyridylmethyl)sulphinyl)-1H-imidazo[4,5-b]pyridine (INN: tenatoprazole).

Brain edema (syn cerebral edema, brain swelling etc.) is a condition with substantial mortality, usually subsequent to e.g. head injuries, tumors, brain surgery or vascular events. Current treatment options such as high dose mannitol infusions, corticosteroids or even craniectomy are not optimal therapies.

A safe drug that can prevent brain edema or reduce the intracranial pressure and which can be used as mono or combination treatment would be a major advantage and could most probably be life-saving for quite a number of patients who untreated might suffer and eventually die from brain edemas.

Description of the invention

It has now been found that these pyridin-2-ylmethylsulphinyl-1H-benzimidazoles and here especially 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole have surprising and advantageous properties when used in the treatment and /or prophylaxis of brain edema.

The invention therefore relates to substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazoles or a pharmaceutically acceptable salt thereof, for the treatment and/or prophylaxis of brain edema.

The invention relates to substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazoles or a pharmaceutically acceptable salt thereof, for use in the treatment of brain edema. The invention relates to substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazoles or a pharmaceutically acceptable salt thereof, for use in the prophylaxis of brain edema.

The invention further relates to a pharmaceutical composition, comprising a substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole or a pharmaceutically acceptable salt thereof, for the treatment and/or prophylaxis of brain edema.

The invention also relates to the use of a substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole or a pharmaceutically acceptable salt thereof in the manufacture of pharmaceutical compositions for the treatment and/or prophylaxis of brain edema.

The invention further relates to a method of treatment or prevention of brain edema comprising administering a therapeutically effective amount of a substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole to a patient in need thereof.

Cerebral edema (syn. brain edema) may be comprehensively defined as a pathologic increase in the amount of total brain water content leading to an increase in brain volume. This deceivingly simple definition fails to reflect the complex pathophysiological underpinnings of the various forms of cerebral edema that may occur in association with severe neurologic diseases.

Edema in the brain may be topographically classified into focal or global. Focal edema generates a pressure gradient with adjacent regions and may result in tissue shift and herniation. Examples of focal edema can be found around tumors, hematomas, and infarctions. Global edema diffusely affects the whole brain and, when critical, it may cause intracranial hypertension, compromise perfusion, and lead to generalized ischemia. Cardiopulmonary arrest, severe traumatic injury, and fulminant liver failure are common causes of global cerebral edema. A different classification based on the pathophysiologic mechanisms responsible for the production of the edema classifies it into 3

types: cytotoxic, vasogenic, and interstitial (for example Rabinstein AA, Treatment of Cerebral Edema, The Neurologist 2006;12: 59–73).

Neurosurgery is a surgical specialty concerned with the treatment of diseases and disorders of the brain, spinal cord, and peripheral and sympathetic nervous system.

Head trauma means injury to the head, scalp and cranium that may be limited to soft tissue damage or may include the cranial bones and the brain. The most common causes of head trauma are traffic accidents, sports injuries, falls, workplace accidents, assaults, and bullet wounds. The head may be damaged both from direct physical injury to the brain and from secondary factors. Secondary factors include lack of oxygen, swelling of the brain, and loss of blood flow to the brain.

Vascular events in the brain are usually referred to as stroke. They occur when blood flow to a region of the brain is disturbed and may result in death of brain tissue. Strokes are a major cause of death and permanent disability. Ischemic stroke is caused by blockage in an artery that supplies blood to the brain, resulting in a deficiency in blood flow (ischemia). Hemorrhagic stroke is caused by the bleeding of ruptured blood vessels (hemorrhage) in the brain.

Accordingly, for the present invention the term brain edema shall be defined to include pathologic effects to the brain resulting from neurosurgery, head trauma, fulminant liver failure or vascular events, as outlined in detail above.

Since the structure of substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazoles includes a chiral center, the compounds can exist as a racemic mixture of enantiomers, a mixture of the corresponding enantiomers independent of their ratio, or an enantiomer being substantially free of the other enantiomer.

Preferably, the substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole is a compound selected from 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulphinyl]-1H-benzimidazole, (S)-5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulphinyl]-1H-benzimidazole, 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole, (S)-5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole, 2-[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)methylsulphinyl]-1H-benzimidazole, 2-{[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]methylsulphinyl}-1H-benzimidazole and 5-methoxy-2-((4-methoxy-3,5-dimethyl-2-pyridylmethyl)sulphinyl)-1H-imidazo[4,5-b]pyridine and pharmaceutically acceptable salts thereof.

Included within the scope of the above given definition for substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazoles are compounds wherein at least one of the hydrogen atoms of one or more substitutents at the benzimidazole or at the pyridinyl moiety of the chemical structure of the compound is substituted by a deuterium atom. Preferably, at least one of

the hydrogen atoms of the substituent at the 4-position of the pyridinyl moiety of the substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole is substituted by a deuterium atom.

More preferred, the substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole is 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole or (S)-5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole and pharmaceutically acceptable salts thereof. Within the scope of the definition of 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole or (S)-5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole are compounds wherein at least one of the hydrogen atoms of one or more substitutents at the benzimidazole or at the pyridinyl moiety of the chemical structure is substituted by a deuterium atom. Preferred within such deuterated compounds are compounds wherein at least one of the hydrogen atoms of the methoxy substituent at the 4-position of the pyridinyl moiety is substituted by a deuterium atom.

"Substantially free" in the context of the invention means that a compound with (S)-configuration and/or its salt contains less than 10 % by weight of a compound with (R)-configuration and/or its salt. Preferably, "substantially free" means that a compound with (S)-configuration and/or its salt contains less than 5 % by weight of a compound with (R)-configuration and/or its salt. More preferably, “substantially free" means that a compound with (S)-configuration and/or its salt contains less than 2 % by weight of a compound with (R)-configuration and/or its salt. In the most preferred embodiment, "substantially free" means that a compound with (S)-configuration and/or its salt contains less than 1 % by weight of a compound with (R)-configuration and/or its salt.

The analogous definition for “substantially free” as described for the (S)-configuration applies vice versa for a compound with (R)-configuration.

Salts of substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazoles include all inorganic and organic acid addition salts and salts with bases, especially all pharmaceutically acceptable inorganic and organic acid addition salts and salts with bases, particularly all pharmaceutically acceptable inorganic and organic acid addition salts and salts with bases customarily used in pharmacy.

Examples of salts with bases include, but are not limited to, lithium, sodium, potassium, calcium, aluminum, magnesium, titanium, ammonium, meglumine and guanidinium salts. Of these, sodium and magnesium are preferred.

Preferred embodiments of the invention might be the sodium salt of 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole, the sodium salt of (S)-5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole, the magnesium salt of 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole or the

magnesium salt of (S)-5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole.

Another embodiments of the invention are also the sodium salt of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulphinyl]-1H-benzimidazole and the magnesium salt of (S)-5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulphinyl]-1H-benzimidazole.

In another embodiment of the invention the salts of the substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazoles may additionally contain water molecules. Examples for such hydrated salts are sodium 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole monohydrate or sesquihydrate, magnesium bis(5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole) dihydrate, or magnesium bis((S)-5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole) dihydrate.

For administering a substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole within the scope of the invention a pharmaceutical composition can be formulated comprising the substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole together with at least one pharmaceutically acceptable auxiliary.

As pharmaceutically acceptable auxiliaries, any auxiliaries known to be suitable for preparing pharmaceutical compositions can be used. Examples thereof include, but are not limited to, solvents, excipients, dispersants, emulsifiers, solubilizers, gel formers, ointment bases, antioxidants, preservatives, stabilizers, carriers, fillers, binders, thickeners, complexing agents, disintegrating agents, buffers, permeation promoters, polymers, lubricants, coating agents, propellants, tonicity adjusting agents, surfactants, colorants, flavorings, sweeteners and dyes. In particular, auxiliaries of a type appropriate to the desired formulation and the desired mode of administration are used.

The pharmaceutical compositions can be formulated, for example, into tablets, coated tablets (dragees), pills, cachets, capsules (caplets), granules, powders, suppositories, solutions (e.g. sterile solutions), emulsions, suspensions, ointments, creams, lotions, pastes, oils, gels, sprays and patches (e.g. transdermal therapeutic systems).

The pharmaceutical compositions comprising the substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole and at least one auxiliary can be manufactured in a manner known to a person skilled in the art, e.g. by dissolving, mixing, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes.

The pharmaceutical compositions can contain a substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole or pharmaceutically acceptable salts thereof as the active compound in a total amount of from 0.1 to 99.9 wt%, preferably 5 to 95 wt%, more preferably 20 to 80 wt%.

The selected formulation depends inter alia on the route of administering the pharmaceutical composition. The pharmaceutical compositions can be administered preferably by any suitable route, but preferably by the oral, intravenous and/or intraarterial route.

Tablets, coated tablets (dragees), pills, cachets, capsules (caplets), granules, solutions, emulsions and suspensions are e.g. suitable for oral administration. In particular, said formulations can be adapted so as to represent, for example, an enteric form, an immediate release form, a delayed release form, a repeated dose release form, a prolonged release form or a sustained release form. Said forms can be obtained, for example, by coating tablets, by dividing tablets into several compartments separated by layers disintegrating under different conditions (e.g. pH conditions) or by coupling the active compound to a biodegradable polymer.

For parenteral modes of administration such as, for example, intravenous, intraarterial, intramuscular, subcutaneous, intracutaneous, intraperitoneal and intrasternal administration, preferably solutions (e.g. sterile solutions, isotonic solutions) are used. They are preferably administered by injection or infusion techniques.

The pharmaceutical composition can be administered in a single dose per day or in multiple subdoses, for example, 2 to 4 doses per day. In case of parental modes of administration, e.g. intraveneous administration continuous administration is preferred, especially if multiple doses are needed. A single dose unit of the pharmaceutical composition can contain e.g. from 0.01 mg to 200 mg, preferably 0.1 mg to 150 mg, more preferably 0.5 mg to 100 mg, most preferably 1 mg to 80 mg, of the active compound.

Another embodiment of the invention is an use of substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazoles in the manufacture of pharmaceutical compositions for the treatment and/ or prophylaxis of brain edema wherein the medicament is administered following a defined scheme.

The (weight) amounts of the substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazoles as given below refer to the free form of the compounds. If a salt form or a hydrated salt form of the substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole is to be administered instead, the (weight) amount of the salt form or hydrated salt form used has to be adapted, i.e. increased accordingly.

A substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole or a pharmaceutically acceptable salt thereof, for the treatment and/or prophylaxis of brain edema, following an administration regime of

a) administering a pharmaceutical composition which contains 40 mg or at least 40 mg of the substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole in a single unit intraveneously at least twice daily for a period of at least three days and up to 28, preferably 14 days,
b) administering a pharmaceutical composition which contains either 20 mg or 40 mg of substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole in a single unit at least twice daily with the provisio that the pharmaceutical composition can be administered to the patient perorally for a remaining period up to 14 days following the administration regime according to step a).

A substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole or a pharmaceutically acceptable salt thereof, for the treatment and/or prophylaxis of brain edema, following an administration regime of

a) administering a pharmaceutical composition which contains 80 mg of the substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole in a single unit intraveneously at least twice daily for a period of at least three days and up to 28, preferably 14 days,
b) administering a pharmaceutical composition which contains either 20 mg or 40 mg of substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole in a single unit at least twice daily with the provisio that the pharmaceutical composition can be administered to the patient perorally for a remaining period up to 14 days following the administration regime according to step a).

The use of a substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole or a pharmaceutically acceptable salt thereof in the manufacture of pharmaceutical compositions for the treatment and/ or prophylaxis of brain edema, following an administration regime of

a) administering a pharmaceutical composition which contains 40 mg or at least 40 mg of the sustituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole in a single unit intraveneously at least twice daily for a period of at least three days and up to 28, preferably 14 days; and
b) administering a pharmaceutical composition which contains either 20 mg or 40 mg of the substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole in a single unit at least twice daily with the provisio that the pharmaceutical composition can be administered to the patient perorally for a remaining period up to 28, preferably 14 days following the administration regime according to step a).

The use of a substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole or a pharmaceutically acceptable salt thereof in the manufacture of pharmaceutical compositions for the treatment and/ or prophylaxis of brain edema, following an administration regime of

a) administering a pharmaceutical composition which contains 80 mg of the sustituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole in a single unit intraveneously at least twice daily for a period of at least three days and up to 28, preferably 14 days; and

b) administering a pharmaceutical composition which contains either 20 mg or 40 mg of the substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole in a single unit at least twice daily with the provisio that the pharmaceutical composition can be administered to the patient perorally for a remaining period up to 28, preferably 14 days following the administration regime according to step a).

The use of a substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole or a pharmaceutically acceptable salt thereof in the manufacture of pharmaceutical compositions for the treatment and/or prophylaxis of brain edema, wherein the pharmaceutical composition is prepared for

a) administering a pharmaceutical composition which contains 40 mg or at least 40 mg of the substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole in a single unit intraveneously at least twice daily for a period of at least three days and up to 28, preferably 14 days; and
b) administering a pharmaceutical composition which contains either 20 mg or 40 mg of the substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole in a single unit at least twice daily with the provisio that the pharmaceutical composition can be administered to the patient perorally for a remaining period up to 28, preferably 14 days following the administration regime according to step a).

The use of a substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole or a pharmaceutically acceptable salt thereof in the manufacture of pharmaceutical compositions for the treatment and/or prophylaxis of brain edema, wherein the pharmaceutical composition is prepared for

a) administering a pharmaceutical composition which contains 80 mg of the substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole in a single unit intraveneously at least twice daily for a period of at least three days and up to 28, preferably 14 days; and
b) administering a pharmaceutical composition which contains either 20 mg or 40 mg of the substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole in a single unit at least twice daily with the provisio that the pharmaceutical composition can be administered to the patient perorally for a remaining period up to 28, preferably 14 days following the administration regime according to step a).

A method of treatment and/or prevention of brain edema comprising administering a therapeutically effective amount of a substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole to a patient in need thereof, comprising the steps of

a) administering a pharmaceutical composition which contains 40 mg or at least 40 mg of the substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole in a single unit intraveneously at least twice daily for a period of at least three days and up to 28, preferably 14 days; and
b) administering a pharmaceutical composition which contains either 20 mg or 40 mg of the substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole in a single unit at least twice daily with the provisio that the pharmaceutical composition can be administered to the patient

perorally for a remaining period up to 28, preferably 14 days following the administration regime according to step a).

A method of treatment and/or prevention of brain edema comprising administering a therapeutically effective amount of a substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole to a patient in need thereof, comprising the steps of

a) administering a pharmaceutical composition which contains 80 mg of the substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole in a single unit intraveneously at least twice daily for a period of at least three days and up to 28, preferably 14 days; and

b) administering a pharmaceutical composition which contains either 20 mg or 40 mg of the substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole in a single unit at least twice daily with the provisio that the pharmaceutical composition can be administered to the patient perorally for a remaining period up to 28, preferably 14 days following the administration regime according to step a).

Preferably, the substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole is a compound selected from 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulphinyl]-1H-benzimidazole, (S)-5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulphinyl]-1H-benzimidazole, 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole, (S)-5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole, 2-[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)methylsulphinyl]-1H-benzimidazole, 2-{[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]methylsulphinyl}-1H-benzimidazole and 5-methoxy-2-((4-methoxy-3,5-dimethyl-2-pyridylmethyl)sulphinyl)-1H-imidazo[4,5-b]pyridine and pharmaceutically acceptable salts thereof.

More preferably, the substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole is a compound selected from 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulphinyl]-1H-benzimidazole, (S)-5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulphinyl]-1H-benzimidazole, 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole, (S)-5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole and pharmaceutically acceptable salts thereof.

A substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole or a pharmaceutically acceptable salt thereof, for the treatment and/or prophylaxis of brain edema, wherein the substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole is 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole, following an administration regime of

a) administering a pharmaceutical composition which contains 40 mg or at least 40 mg of 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole in a single unit intraveneously at least twice daily for a period of at least three days and up to 28, preferably 14 days,

b) administering a pharmaceutical composition which contains either 20 mg or 40 mg of 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole in a single unit at least twice daily with the provisio that the pharmaceutical composition can be administered to the patient perorally for a remaining period up to 28, preferably 14 days following the administration regime according to step a).

A substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole or a pharmaceutically acceptable salt thereof, for the treatment and/or prophylaxis of brain edema, wherein the substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole is 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole, following an administration regime of

a) administering a pharmaceutical composition which contains 80 mg of 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole in a single unit intraveneously at least twice daily for a period of at least three days and up to 28, preferably 14 days,

b) administering a pharmaceutical composition which contains either 20 mg or 40 mg of 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole in a single unit at least twice daily with the provisio that the pharmaceutical composition can be administered to the patient perorally for a remaining period up to 28, preferably 14 days following the administration regime according to step a).

The use of a substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole or a pharmaceutically acceptable salt thereof in the manufacture of pharmaceutical compositions for the treatment and/ or prophylaxis of brain edema, wherein the the substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole is 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole, following an administration regime of

a) administering a pharmaceutical composition which contains 40 mg or at least 40 mg of 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole in a single unit intraveneously at least twice daily for a period of at least three days and up to 28, preferably 14 days; and

b) administering a pharmaceutical composition which contains either 20 mg or 40 mg of 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole in a single unit at least twice daily with the provisio that the pharmaceutical composition can be administered to the patient perorally for a remaining period up to 28, preferably 14 days following the administration regime according to step a).

The use of a substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole or a pharmaceutically acceptable salt thereof in the manufacture of pharmaceutical compositions for the treatment and/ or prophylaxis of brain edema, wherein the the substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole is 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole, following an administration regime of

a) administering a pharmaceutical composition which contains 80 mg of 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole in a single unit intraveneously at least twice daily for a period of at least three days and up to 28, preferably 14 days; and

b) administering a pharmaceutical composition which contains either 20 mg or 40 mg of 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole in a single unit at least twice daily with the provisio that the pharmaceutical composition can be administered to the patient perorally for a remaining period up to 28, preferably 14 days following the administration regime according to step a).

The use of a substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole or a pharmaceutically acceptable salt thereof in the manufacture of pharmaceutical compositions for the treatment and/or prophylaxis of brain edema, wherein the the substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole is 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole, and wherein the pharmaceutical composition is prepared for

a) administering a pharmaceutical composition which contains 40 mg or at least 40 mg of 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole in a single unit intraveneously at least twice daily for a period of at least three days and up to 28, preferably 14 days; and

b) administering a pharmaceutical composition which contains either 20 mg or 40 mg of 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole in a single unit at least twice daily with the provisio that the pharmaceutical composition can be administered to the patient perorally for a remaining period up to 28, preferably 14 days following the administration regime according to step a).

The use of a substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole or a pharmaceutically acceptable salt thereof in the manufacture of pharmaceutical compositions for the treatment and/or prophylaxis of brain edema, wherein the the substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole is 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole, and wherein the pharmaceutical composition is prepared for

a) administering a pharmaceutical composition which contains 80 mg of 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole in a single unit intraveneously at least twice daily for a period of at least three days and up to 28, preferably 14 days; and

b) administering a pharmaceutical composition which contains either 20 mg or 40 mg of 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole in a single unit at least twice daily with the provisio that the pharmaceutical composition can be

administered to the patient perorally for a remaining period up to 28, preferably 14 days following the administration regime according to step a).

A method of treatment or prevention of brain edema comprising administering a therapeutically effective amount of a substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole to a patient in need thereof, wherein the the substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole is 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole, comprising the steps of:

a) administering a pharmaceutical composition which contains 40 mg or at least 40 mg of 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole in a single unit intraveneously at least twice daily for a period of at least three days and up to 28, preferably 14 days; and

b) administering a pharmaceutical composition which contains either 20 mg or 40 mg of 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole in a single unit at least twice daily with the provisio that the pharmaceutical composition can be administered to the patient perorally for a remaining period up to 28, preferably 14 days following the administration regime according to step a).

A method of treatment or prevention of brain edema comprising administering a therapeutically effective amount of a substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole to a patient in need thereof, wherein the the substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole is 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole, comprising the steps of:

a) administering a pharmaceutical composition which contains 80 mg of 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole in a single unit intraveneously at least twice daily for a period of at least three days and up to 28, preferably 14 days; and

b) administering a pharmaceutical composition which contains either 20 mg or 40 mg of 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole in a single unit at least twice daily with the provisio that the pharmaceutical composition can be administered to the patient perorally for a remaining period up to 28, preferably 14 days following the administration regime according to step a).

Preferably, a single unit of the substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole as administered to the patient in step b) is suitably provided as a peroral pharmaceutical composition, advantageously in an enteric coated form.

Biological investigations

In a randomized, double-blind and placebo-controlled clinical study, initially targeted to gain an better understanding of the effectiveness of the use of pantoprazole in the prevention of stress induced upper gastrointestinal bleeding in neurosurgical or head trauma patients it was observed that a statistically significant effect on the reduced occurrence of brain edema can be achieved.

According to the study protocoll, from day 1 to day 3 pantoprazole 80 mg was given intravenous every 12 hours and continued thereafter until a peroral intake was initiated. The peroral dosage regime was pantoprazole 40 mg every 12 hours until day 14 of the study.

An evaluation of the study results revealed that from the 22 patients in the placebo arm of the study five patients (18.2 %) suffered from brain edema during the treatment period. In contrast hereto only one out of 45 patients (2.2 %) in the pantoprazole arm of the study was diagnosed with a brain edema during the treating period.

Claims

1. A substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole or a pharmaceutically acceptable salt thereof, for the treatment and/or prophylaxis of brain edema.

2. A substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole according to claim 1, wherein the brain edema is a brain edema resulting from neurosurgery, head trauma, fulminant liver failure or vascular events.

3. A substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole according to claim 1, wherein the substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole is selected from 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulphinyl]-1H-benzimidazole, (S)-5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulphinyl]-1H-benzimidazole, 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole, 2-[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)methylsulphinyl]-1H-benzimidazole, 2-{[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]methylsulphinyl}-1H-benzimidazole or 5-methoxy-2-((4-methoxy-3,5-dimethyl-2-pyridylmethyl)sulphinyl)-1H-imidazo[4,5-b]pyridine.

4. A substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole according to claim 1, wherein the substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole is 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulphinyl]-1H-benzimidazole or (S)-5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulphinyl]-1H-benzimidazole.

5. A substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole according to claim 1, wherein the substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole is 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole , following a regime of

   a) administering a pharmaceutical composition which contains 40 mg or at least 40 mg of 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole in a single unit intraveneously at least twice daily for a period of at least three days and up to 28, preferably 14 days; and
   b) administering a pharmaceutical composition which contains either 20 mg or 40 mg of 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole in a single unit at least twice daily with the provisio that the pharmaceutical composition can be administered to the patient perorally for a remaining period up to 28, preferably 14 days following the administration regime according to step a).

6. A substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole according to claim 1, wherein the substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole is 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole , following a regime of

a) administering a pharmaceutical composition which contains 80 mg of 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole in a single unit intraveneously at least twice daily for a period of at least three days and up to 28, preferably 14 days; and

b) administering a pharmaceutical composition which contains either 20 mg or 40 mg of 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole in a single unit at least twice daily with the provisio that the pharmaceutical composition can be administered to the patient perorally for a remaining period up to 28, preferably 14 days following the administration regime according to step a).

7. A substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole according to claim 1, wherein the substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole is 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole or (S)- 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulphinyl]-1H-benzimidazole.

8. A substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole or a pharmaceutically acceptable salt thereof, for use in the prophylaxis of brain edema.

9. A substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole or a pharmaceutically acceptable salt thereof, for use in the treatment of brain edema.

10. A method of treatment or prevention of brain edema by administering a therapeutically effective amount of a substituted pyridin-2-ylmethylsulphinyl-1H-benzimidazole to a patient in need thereof.