WO 2004/098597 A1

Title: COMPOSITION COMPRISING ROFLUMILAST AND SHU511R II

Abstract: The invention relates to the combined administration of roflumilast and shu511R II for the treatment of a disease in which phosphodiesterase-4 (PDE4) and/or interleukin-1 (IL-1) activity is detrimental.
Composition comprising Roflumilast and shuIL-1R II

Field of application of the invention

The invention relates to the combination of certain known active compounds for therapeutic purposes. The substances used in the combination according to the invention are known active compounds from the PDE4 inhibitor class and known active compounds from the interleukin-1 (IL-1) antagonist class. Their combined use in the sense according to the invention for therapeutic purposes has not yet been described in the prior art.

Prior art

In the international patent application WO95/01388 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloropyrid-4-yl)benzamide (INN: ROFLUMILAST), its N-Oxide and the use of these compounds as selective PDE4 inhibitors is described. In the International patent application WO03/38552 the combination of Roflumilast with several disease modifying anti-rheumatic drugs (DMARDs) is disclosed. In the Journal of Pharmacology and Experimental Therapeutics Vol. 297, 2001 pp. 267-279 and 280-290 the anti-inflammatory and immunomodulatory potential of Roflumilast in vitro, and its in vivo efficacy in airway disease models is described. In Emerging Drugs Vol. 5, 2000 pp. 309-319 the use of PDE4 inhibitors in the treatment of chronic obstructive pulmonary disease is reviewed. In the International patent application WO91/18982 the preparation of soluble Type II Interleukin-1 receptors and their use for regulating an IL-1 mediated immune or inflammatory response in a mammal is described.

Summary of the invention

The invention relates to pharmaceutical compositions and methods for preventing or reducing the onset of symptoms of a disease in which phosphodiesterase 4 (PDE4) and/or interleukin-1 (IL-1) activity is detrimental, or treating or reducing the severity of a disease in which phosphodiesterase 4 (PDE4) and/or interleukin-1 (IL-1) activity is detrimental.

In particular it relates to compositions and methods for treating a disease mediated by phosphodiesterase 4 (PDE4) and/or interleukin-1 (IL-1) activity by administering a PDE4 inhibitor in combination with an IL-1 antagonist.

In this connection, it is the object of the present invention to make available a certain anti-inflammatory therapeutic, which fulfills the following conditions:
- Pronounced anti-inflammatory action
- Minor side effects
- Good suitability for long-term therapy

It has now been found that the combined use of the PDE4 inhibitor roflumilast and Immunex's soluble human Type II Interleukin-1 receptor (shuIL-1R II) outstandingly fulfills the abovementioned conditions.

Accordingly, the invention relates in a first aspect to a method for preventing or reducing the onset of symptoms of a disease in which phosphodiesterase 4 (PDE4) and/or interleukin-1 (IL-1) activity is detrimental, or treating or reducing the severity of a disease in which phosphodiesterase 4 (PDE4) and/or interleukin-1 (IL-1) activity is detrimental by administering to a patient in need thereof simultaneously an effective amount of (1) roflumilast and (2) shuIL-1R II.

In a second aspect the invention relates to a method for preventing or reducing the onset of symptoms of a disease in which phosphodiesterase 4 (PDE4) and/or interleukin-1 (IL-1) activity is detrimental, or treating or reducing the severity of a disease in which phosphodiesterase 4 (PDE4) and/or interleukin-1 (IL-1) activity is detrimental by administering to a patient in need thereof in succession, close in time or remote in time, in any order whatever an effective amount of (1) roflumilast and (2) shuIL-1R II.

The invention also relates to a pharmaceutical composition for preventing or reducing the onset of symptoms of a disease in which phosphodiesterase 4 (PDE4) and/or interleukin-1 (IL-1) activity is detrimental, or treating or reducing the severity of a disease in which phosphodiesterase 4 (PDE4) and/or interleukin-1 (IL-1) activity is detrimental, comprising as a fixed combination an effective amount of

(a) roflumilast and
(b) shuIL-1R II and optionally
(c) a pharmaceutically acceptable carrier.

The invention further relates to a pharmaceutical composition for preventing or reducing the onset of symptoms of a disease in which phosphodiesterase 4 (PDE4) and/or interleukin-1 (IL-1) activity is detrimental, or treating or reducing the severity of a disease in which phosphodiesterase 4 (PDE4) and/or interleukin-1 (IL-1) activity is detrimental, comprising as a free combination an effective amount of

(a) roflumilast and optionally a pharmaceutically acceptable carrier and
(b) shuIL-1R II and optionally a pharmaceutically acceptable carrier.

The invention additionally relates to a method for preparing a pharmaceutical composition which is effective for preventing or reducing the onset of symptoms of a disease in which phosphodiesterase 4
(PDE4) and/or interleukin-1 (IL-1) activity is detrimental, or treating or reducing the severity of a disease in which phosphodiesterase 4 (PDE4) and/or interleukin-1 (IL-1) activity is detrimental, which method comprises mixing an effective amount of roflumilast and shuIL-1R II with a pharmaceutically acceptable carrier.

The invention furthermore relates to the use of a combination of roflumilast and shuIL-1R II for the preparation of a pharmaceutical composition for preventing or reducing the onset of symptoms of a disease in which phosphodiesterase 4 (PDE4) and/or interleukin-1 (IL-1) activity is detrimental, or treating or reducing the severity of a disease in which phosphodiesterase 4 (PDE4) and/or interleukin-1 (IL-1) activity is detrimental.

**Detailed description of the invention**

The combination therapy, which is the subject matter of this invention comprises administering roflumilast with shuIL-1R II to prevent onset of a disease in which phosphodiesterase 4 (PDE4) and/or interleukin-1 (IL-1) activity is detrimental or to treat such an existing condition.

The invention thus relates to the combined use of roflumilast and shuIL-1R II in preventing the symptoms of, or treating a disease in which phosphodiesterase 4 (PDE4) and/or interleukin-1 (IL-1) activity is detrimental.

In the sense of the invention, the term "roflumilast" is understood to include the pharmaceutically acceptable salts and the N-oxide of ROFLUMILAST, which can likewise be used according to the invention.

ROFLUMILAST is the international non proprietary name (INN) for 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloropyrid-4-yl)benzamide [structure of formula (1.1)]. The preparation of 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloropyrid-4-yl)benzamide, its pharmaceutically acceptable salts and its N-oxide [3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloro-1-oxypyrid-4-yl)benzamide; structure of formula (1.2)] as well as the use of these compounds as phosphodiesterase (PDE) 4 inhibitors is described in WO95/01338.
Suitable pharmaceutically acceptable salts of ROFLUMILAST are in particular water-soluble and water-insoluble acid addition salts with acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulfuric acid, acetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-hydroxybenzoyl)-benzoic acid, butyric acid, sulfosalicylic acid, maleic acid, laurie acid, malic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, embonic acid, stearic acid, toluenesulfonic acid, methanesulfonic acid or 1-hydroxy-2-naphthol acid, the acids being employed in salt preparation - depending on whether it is a mono- or polybasic acid and depending on which salt is desired - in an equimolar quantitative ratio or one differing therefrom.

It is understood that the active compounds and their pharmaceutically acceptable salts mentioned can also be present, for example, in the form of their pharmaceutically acceptable solvates, in particular in the form of their hydrates.

In the sense of the invention, the term "shuIL-1R II" is understood to represent a soluble human Type II interleukin-1 receptor of Immunex. The preparation and use of soluble human Type II interleukin-1 receptors is described in USP5,767,064.

"Diseases in which phosphodiesterase 4 (PDE4) and/or interleukins-1 (IL-1) activity is detrimental" which may be mentioned are in particular acute and chronic (in particular inflammatory and allergen-induced) airway disorders of varying origin (bronchitis, allergic bronchitis, chronic bronchitis, bronchial asthma, severe bronchial asthma, emphysema, COPD, pulmonary sarcoidosis, pulmonary fibrosis, silicosis); dermatoses (especially of proliferative, inflammatory and allergic type) such as psoriasis (vulgaris), toxic and allergic contact eczema, atopic eczema, seborrhoeic eczema, Lichen simplex, sunburn, pruritus in the anogenital area, alopecia areata, hypertrophic scars, discoid lupus erythematosus, follicular and widespread pyodermias, endogenous and exogenous acne, acne rosacea and other proliferative, inflammatory and allergic skin disorders; disorders which are based on an excessive release of TNF and leukotrienes, for example disorders of the arthritis type (rheumatoid arthritis, psoriatic arthritis, juvenile rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions), spondylarthropathies (ankylosing spondylitis), Wegener's granulomatosis, adult Still's disease, Behcet's disease, polymyositis, myelodysplastic syndrome, scleroderma, dermatomyositis, Sjogren's syndrome, disorders of the immune system (AIDS), autoimmune diseases (e.g., Multiple Sclerosis, allergy, autoimmune uveitis
and nephritic syndrome), transplant rejection, including rejections of allografts and xenografts, graft versus host disease, types of shock [septic shock, endotoxin shock, gram-negative sepsis, toxic shock syndrome and ARDS (adult respiratory distress syndrome)] and also generalized inflammations in the gastrointestinal region (Inflammatory bowel disease, Crohn's disease and ulcerative colitis); disorders which are based on allergic and/or chronic, immunological false reactions in the region of the upper airways (pharynx, nose) and the adjacent regions (paranasal sinuses, eyes), such as allergic rhinitis/sinusitis, chronic rhinitis/sinusitis, allergic conjunctivitis and also nasal polyps; but also disorders of the heart which can be treated by PDE and/or TNFα inhibitors, such as cardiac insufficiency, ischemia of the heart and congestive heart failure, or disorders which can be treated on account of the tissue-relaxant action of the PDE inhibitors, such as colics of the kidneys and of the ureters in connection with kidney stones. The pharmaceutical compositions according to the invention can furthermore be used in the treatment of conditions associated with cerebral metabolic inhibition, such as cerebral senility, senile dementia (Alzheimer's disease), memory impairment associated with Parkinson's disease or multiinfarct dementia; in the treatment of malignancies to inhibit tumor growth, or metastasis, and/or to alleviate cachexia secondary to malignancy; in the treatment of infectious diseases like bacterial meningitis, cachexia or cerebral malaria; and in the treatment of diseases like inflammatory bone disease, bone resorption disease, hepatitis, viral hepatitis, reperfusion injury, scar tissue formation, pyrexia, periodontal disease and radiation toxicity. The pharmaceutical compositions according to the invention can as well be used in the treatment of chronic fever syndromes, metabolic syndrome and sequelae, e.g. type 2 diabetes.

The phrase "combined use" (or "combination") embraces the administration of rolumilast and shuL-1R II as part of a specific treatment regimen intended to provide a beneficial effect from the co-action of these therapeutic agents. Administration of these therapeutic agents in combination typically is carried out over a defined time period (usually, minutes, hours, days or weeks depending upon the combination selected). "Combined use" generally is not intended to encompass the administration of two of these therapeutic agents as part of separate monotherapy regimens that incidentally and arbitrarily result in the combinations of the present invention.

"Combined use" or "combination" within the meaning of the present invention is to be understood as meaning that the individual components can be administered simultaneously (in the form of a combination medicament – fixed combination) or more or less simultaneously, respectively in succession (from separate pack units – free combination; directly in succession or else alternatively at a relatively large time interval). As an example, one therapeutic agent could be taken in the morning and one later in the day. Or in another scenario, one therapeutic agent could be taken once daily and the other once daily or once weekly.

Simultaneous administration preferably is accomplished by administering to the subject in need thereof, for example, a single intravenous injection having a fixed ratio of each therapeutic agent. More or less simultaneous administration or administration in succession of each therapeutic agent can be effected by any appropriate route, including, but not limited to, oral routes, intravenous routes,
intramuscular routes, and by infusion techniques. The therapeutic agents can be administered by the same route or by different routes. For example, a first therapeutic agent of the combination selected may be administered by intravenous or subcutaneous injection while the other therapeutic agent of the combination may be administered orally. The sequence in which the therapeutic agents are administered is not narrowly critical.

The therapeutic agent(s) according to the invention may be administered in a variety of forms. These include, for example, liquid, semi-solid and solid dosage forms, such as liquid solutions (e.g., injectable and infusible solutions), dispersions or suspensions, tablets, pills, powders, liposomes or suppositories. The preferred form depends on the intended mode of administration and therapeutic application.

The most preferred mode of administration of roflumilast is oral. In another preferred embodiment roflumilast is administered by intravenous infusion or injection. In a further embodiment roflumilast is administered by intramuscular or subcutaneous injection. Other routes of administration are also contemplated, including intranasal and transdermal routes, and by inhalation.

Purified soluble type II IL-1R protein compositions preferably are administered by bolus injection, continuous infusion, sustained release from implants. Typically, a soluble type II IL-1R therapeutic agent will be administered in the form of a composition comprising purified protein in conjunction with physiologically acceptable carriers, excipients or diluents. Such carriers will be nontoxic to recipients at the dosages and concentrations employed. Ordinarily, the preparation of such compositions entails combining the type II IL-1R with buffers, antioxidants such as ascorbic acid, low molecular weight (less than about 10 residues) polypeptides, proteins, amino acids, carbohydrates including glucose, sucrose or dextrins, chelating agents such as EDTA, glutathione and other stabilizers and excipients. Neutral buffered saline or saline mixed with conspecific serum albumin are exemplary appropriate diluents. Preferably, product is formulated as a lyophilize using appropriate excipient solutions (e.g., sucrose) as diluents.

Therapeutic compositions typically must be sterile and stable under the condition of manufacture and storage. The composition can be formulated, for example, as a solution, microemulsion, dispersion, liposome, or other ordered structure suitable to high drug concentration.

Sterile injectable solutions can be prepared by incorporating the therapeutic agent(s) in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the therapeutic agent(s) into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying that yields a powder of the therapeutic agent(s) plus any additional desired ingredient from the prev-
ously sterile filtered solution thereof. The proper fluidity of a solution can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prolonged absorption of injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, monostearate salts and gelatin.

The therapeutic agent(s) of the present invention can be administered by a variety of methods known in the art, although for many therapeutic applications, the preferred route of administration for a fixed combination of roflumilast and the shuL-1R II according to the invention is intravenous injection or infusion.

In certain embodiments, the therapeutic agent(s) may be prepared with a carrier that will protect the agent against rapid release, such as a controlled release formulation, including implants, transdermal patches, and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Many methods for the preparation of such formulations are generally known to those skilled in the art.

In certain embodiments, the therapeutic agent(s) of the invention may be orally administered, for example, with an inert diluent or an assimilable edible carrier. The therapeutic agent(s) may also be enclosed in a hard or soft shell gelatine capsule or compressed into tablets. For oral therapeutic administration the therapeutic agent(s) may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. To administer the therapeutic agent(s) according to the invention it may be necessary to coat the therapeutic agent(s) with, or co-administer with the therapeutic agent(s) with, a material to prevent its inactivation.

The therapeutic agent(s) are dosed in an order of magnitude customary for the individual dose, it more likely being possible, on account of the individual actions, which are mutually positively influencing and reinforcing, to reduce the respective doses on the combined administration of the therapeutic agent(s) with the norm.

In case of oral administration of 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloropyrid-4-yl)-benzamide (ROFLUMILAST), the adult daily dose is in the range from 50 – 1000μg, preferably in the range from 250 – 500μg, preferably by once daily administration.

In case of subcutaneous administration of 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloropyrid-4-yl)benzamide (ROFLUMILAST), the adult daily dose is in the range from 50 – 1000μg, preferably in the range from 250 – 500μg.
In case of intravenous administration of 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloropyrid-4-yl)benzamide (ROFLUMILAST), the adult daily dose is in the range from 50 – 600μg, preferably in the range from 150 – 300μg.

An exemplary, non-limiting range for the soluble human Type II interleukin-1 receptor is from about 1 ng/kg/day to about 10 mg/kg/day, and more preferably from about 500 μg/kg/day to about 5 mg/kg/day.
Patent claims

1. Combined use of roflumilast and shuIL-1R II for preventing or reducing the onset of symptoms of, or treating or reducing the severity of a disease in which phosphodiesterase 4 (PDE4) and/or interleukin-1 (IL-1) activity is detrimental, in a patient in need thereof.

2. Pharmaceutical composition suited for the combined use according to claim 1, comprising as a fixed combination an effective amount of
   (a) roflumilast and
   (b) shuIL-1R II and optionally
   (c) a pharmaceutically acceptable carrier.

3. Pharmaceutical composition according to claim 2, which is a fixed injectable combination.

4. Pharmaceutical composition suited for the combined use according to claim 1, comprising as a free combination an effective amount of
   (a) roflumilast and optionally a pharmaceutically acceptable carrier and
   (b) shuIL-1R II and optionally a pharmaceutically acceptable carrier.

5. Method for preventing or reducing the onset of symptoms of a disease in which phosphodiesterase 4 (PDE4) and/or interleukin-1 (IL-1) activity is detrimental, or treating or reducing the severity of a disease in which phosphodiesterase 4 (PDE4) and/or interleukin-1 (IL-1) activity is detrimental by administering to a patient in need thereof simultaneously an effective amount of (1) roflumilast and (2) shuIL-1R II.

6. Method for preventing or reducing the onset of symptoms of a disease in which phosphodiesterase 4 (PDE4) and/or interleukin-1 (IL-1) activity is detrimental, or treating or reducing the severity of a disease in which phosphodiesterase 4 (PDE4) and/or interleukin-1 (IL-1) activity is detrimental by administering to a patient in need thereof in succession, close in time or remote in time, in any order whatever an effective amount of (1) roflumilast and (2) shuIL-1R II.

7. Use of a combination of roflumilast and shuIL-1R II for the preparation of a pharmaceutical composition for preventing or reducing the onset of symptoms of a disease in which phosphodiesterase 4 (PDE4) and/or interleukin-1 (IL-1) activity is detrimental, or treating or reducing the severity of a disease in which phosphodiesterase 4 (PDE4) and/or interleukin-1 (IL-1) activity is detrimental.

8. Pharmaceutical composition, use or method according to any of claims 1 to 7, wherein roflumilast represents 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloropyrid-4-yl)benzamide.
9. Pharmaceutical composition, use or method according to any of claims 1 to 7, wherein roflumilast represents 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloro-1-oxo-pyrid-4-yl)benzamide.

10. Pharmaceutical composition, use or method according to any of claims 1 to 9, wherein the disease in which phosphodiesterase 4 (PDE4) and/or interleukin-1 (IL-1) activity is detrimental is selected from rheumatoid arthritis, psoriasis, psoriatic arthritis, juvenile arthritis, inflammatory bowel disease, spondylarthropathies (ankylosing spondylitis), adult-onset Still’s disease, Behcet’s disease, polymyositis, sarcoidosis, Wegener granulomatosis, myelodysplastic syndrome, inflammatory myositis, Sjögren syndrome, severe chronic asthma, septic shock, uveitis and graft versus host disease.

11. Pharmaceutical composition, use or method according to any of claims 1 to 9, wherein the disease in which phosphodiesterase 4 (PDE4) and/or interleukin-1 (IL-1) activity is detrimental is selected from rheumatoid arthritis, psoriasis, psoriatic arthritis, juvenile arthritis, inflammatory bowel disease and spondylarthropathies (ankylosing spondylitis).
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/44 A61K38/17 A61P43/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, MEDLINE, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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