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Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AL, AU, BA, BR, CA, CN, CO, DZ, EC, EG, GE, HR, ID, IL, IN, IS, JP, KR, LT, LV, MA, MK, MX, NO, NZ, PH, PL, SG, TN, UA, VN, YU, ZA, ZW, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR)*
— *of inventorship (Rule 4.17(iv)) for US only*

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(54) Title: SYNERGISTIC COMBINATION COMPRESING ROFLUMILAS AND (R.R) -FORMOTEROL

(57) Abstract: The invention relates to the combined administration of roflumilast and R,R-formoterol for the treatment of respiratory tract disorders.

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SYNERGISTIC COMBINATION COMPRISING ROFLUMILAST AND (R,R)-FORMOTEROL

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 a known active compound from the PDE inhibitors class and an active compound from the β_2 adrenoceptor agonists 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

International patent application WO01/13953 (US Patent 6,624,181) describes the combination of a compound from the class of PDE inhibitors with a compound from the class of β_2 adrenoceptor agonists for the treatment of respiratory tract disorders. – United States patent 6,288,118 generally describes the treatment of pulmonary diseases, such as chronic obstructive pulmonary disease or asthma, by administering a phosphodiesterase-4 inhibitor with a beta-adrenergic bronchodilator. – In Current Opinion in Investigational Drugs 2002 3(8): 1165-1170, the PDE4-inhibitor Roflumilast is described in detail. – In International patent application WO98/35683 a composition containing lung surfactant and Roflumilast is described. – In the review Expert Opin. Ther. Patents (2002) 12(1): 53-63 the patent literature during the period January 1998 to August 2001 concerning bronchodilators is analyzed, and exemplary compounds for the different substance classes are named, inter alia the PDE4-inhibitor Roflumilast. – United States patent 5,795,564 discloses a method and composition utilizing the pure (R, R) isomer of formoterol. – In International patent applications WO02/066422 and WO02/076933 certain new β_2 adrenoceptor agonists and their use in respiratory tract disorders are disclosed. - In International patent application WO00/67741 the pure (S, R) isomer of formoterol and its use is disclosed. - In International patent application WO02/088167 certain Androstane derivatives and combinations thereof with e.g. β_2 adrenoceptor agonists are described.

Summary of the invention

The invention relates to compositions and methods for preventing or reducing the onset of symptoms of pulmonary diseases, or treating or reducing the severity of pulmonary diseases. In particular it relates to compositions and methods for treating pulmonary diseases mediated by phosphodiesterase 4 (PDE4) by administering a PDE4 inhibitor together with another pharmaceutically active agent, which

affects pulmonary function. In this connection, it is the object of the present invention to make available a certain respiratory tract therapeutic which fulfills the following conditions:

- Pronounced antiinflammatory action
- Distinct bronchorelaxation and -dilatation
- Good oral availability, at least with respect to the PDE4 inhibitor
- Minor side effects
- Good suitability for long-term therapy
- Favorable influence on bronchial hyperreactivity.

It has now been found that the combined use of the PDE4 inhibitor roflumilast and of the β_2 adrenoceptor agonist R,R-formoterol outstandingly fulfills the abovementioned conditions, in particular in view of the fact that the combination of the two compounds acts synergistically, i. e. exhibits a greater than additive effect.

Accordingly, the invention relates in a first aspect to a method for preventing or reducing the onset of symptoms of a pulmonary disease, or treating or reducing the severity of a pulmonary disease by administering to a patient in need thereof an effective amount of roflumilast and R,R-formoterol either in a single combined form, separately, or separately and sequentially where the sequential administration is close in time, or remote in time.

The invention also relates to a composition for preventing or reducing the onset of symptoms of a pulmonary disease, or treating or reducing the severity of a pulmonary disease comprising an effective amount of roflumilast, an effective amount of R,R-formoterol and a pharmaceutically acceptable excipient.

The invention additionally relates to a method for preparing a composition which is effective for preventing or reducing the onset of symptoms of a pulmonary disease, or treating or reducing the severity of a pulmonary disease, which method comprises mixing an effective amount of roflumilast and R,R-formoterol with a pharmaceutically acceptable excipient.

Detailed description of the invention

The combination therapy which is the subject matter of this invention comprises administering roflumilast with R,R-formoterol to prevent onset of a pulmonary disease event or to treat an existing condition. The two compounds may be administered together in a single dosage form. Or they may be administered in different dosage forms. They may be administered at the same time. Or they may be administered both close in time or remotely, such as where one drug is administered in the morning

and the second drug is administered in the evening. The combination may be used prophylactically or after the onset of symptoms has occurred. In some instances the combination may be used to prevent the progression of a pulmonary disease or to arrest the decline of a function such as lung function.

The invention thus relates to the combined use of roflumilast and R,R-formoterol in preventing the symptoms of, or treating a respiratory tract disorder.

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

Correspondingly, the term "R,R-formoterol" is understood in connection with this invention to include the pharmacologically acceptable salts of R,R-formoterol.

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

Suitable pharmacologically acceptable salts of roflumilast or R,R-formoterol 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, lauric acid, malic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, embonic acid, stearic acid, toluenesulfonic acid, methanesulfonic acid or 1-hydroxy-2-naphthoic 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. A particularly preferred salt of R,R-formoterol is the fumarate.

Respiratory tract disorders which may be mentioned are in particular allergen- and inflammation-induced bronchial disorders (bronchitis, obstructive bronchitis, spastic bronchitis, allergic bronchitis, allergic asthma, bronchial asthma, COPD), which can be treated by the combination according to the invention also in the sense of a long-term therapy (if desired with appropriate adjustment of the dose of the individual components to the needs at the time, for example needs subject to seasonally related variations).

"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), more or less simultaneously (from separate pack units) or in succession (directly in succession or else alternatively at a relatively large time interval) in a manner which is known per se and customary. As an example, one drug could be taken in the morning and one later in the day. Or in another scenario, one drug could be taken twice daily and the other once daily, either at the same

time as one of the twice-a-day dosing occurred, or separately.

"Combined use" or "combination" within the meaning of the present invention is particularly to be understood as meaning that the two components act together in a synergistic manner.

R,R-formoterol is usually administered as an oral or nasal spray or aerosol, or as an inhaled powder. Usually R,R-formoterol is not administered systemically or by injection. Roflumilast can be administered orally or by inhalation (orally or internasally). This invention contemplates either co-administering both drugs in one delivery form such as an inhaler, which is putting both drugs in the same inhaler. Alternatively one can put roflumilast into pills and package them in a medicament pack with an inhaler that contains R,R-formoterol.

Within the meaning of the present invention, "use" can thus be understood as meaning primarily with respect to roflumilast the oral administration. In view of the synergistic effect of the combined use according to the invention, it is possible to use R,R-formoterol orally in a lower dose, avoiding thus the known side effects of orally administered R,R-formoterol in higher doses. With respect to R,R-formoterol, "use" is therefore, in accordance with the invention, understood primarily as meaning the oral administration, but it is also understood to mean topical application in inhalatory form. For inhalation, R,R-formoterol is preferably administered in the form of an aerosol, the aerosol particles of solid, liquid or mixed composition having a diameter of 0.5 to 10 µm, advantageously of 2 to 6 µm.

Aerosol generation can be carried out, for example, by pressure-driven jet atomizers or ultrasonic atomizers, but advantageously by propellant-driven metered aerosols or propellant-free administration of micronized active compounds from inhalation capsules.

The active compounds 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 active compounds compared with the norm. For inhalation, R,R-formoterol is intended to be administered in a dose of preferably 10 to 50 µg per day by once, twice or three times daily administration.

Depending on the inhaler system used, in addition to the active compound the administration forms additionally contain the required excipients, such as, for example, propellants (e.g. Frigen in the case of metered aerosols), surface-active substances, emulsifiers, stabilizers, preservatives, flavorings, fillers (e.g. lactose in the case of powder inhalers) or, if appropriate, further active compounds.

For the purposes of inhalation, a large number of apparatuses are available with which aerosols of optimum particle size can be generated and administered, using an inhalation technique which is as right as possible for the patient. In addition to the use of adaptors (spacers, expanders) and pear-

shaped containers (e.g. Nebulator®, Volumatic®), and automatic devices emitting a puffer spray (Autohaler®), for metered aerosols, in particular in the case of powder inhalers, a number of technical solutions are available (e.g. Diskhaler®, Rotadisk®, Turbohaler® or the inhaler described in European Patent Application EP 0 505 321), using which an optimal administration of active compound can be achieved.

In the case of the oral administration of R,R-formoterol, which is the preferred administration form in the combined use according to the invention, the daily dose is in the range from 20 to 120 µg per day by once, twice or three times daily oral administration.

In the case of the oral administration of roflumilast, which is the preferred administration form, the daily dose is in the range from 100 to 500 µg per day, preferably by once daily oral administration.

In case of medicaments which are intended for oral administration, the active ingredients roflumilast and/or R,R-formoterol are formulated to give medicaments according to processes known per se and familiar to the person skilled in the art. The active ingredients are employed as medicament, preferably in combination with suitable pharmaceutical excipients or vehicles, in the form of tablets, coated tablets, capsules, emulsions, suspensions or solutions, the active compound content advantageously being between 0.1 and 95% and, by the appropriate choice of the excipients and vehicles, it being possible to achieve a pharmaceutical administration form precisely tailored to the active compound(s) and/or to the desired onset of action (e.g. a sustained-release form or an enteric form). In case of a once daily oral administration of both roflumilast and R,R-formoterol in an oral single unit dosage form, R,R-formoterol is preferably formulated in such a way that it is released during a prolonged period of time.

The person skilled in the art is familiar on the basis of his/her expert knowledge with, which excipients or vehicles are suitable for the desired pharmaceutical formulations. In addition to solvents, gel-forming agents, tablet excipients and other active compound carriers, it is possible to use, for example, antioxidants, dispersants, emulsifiers, antifoams, flavor corrigents, preservatives, solubilizers, colorants or permeation promoters and complexing agents (e.g. cyclodextrins).

Patent claims

1. Combined use of roflumilast and R,R-formoterol in preventing the symptoms of, or treating a respiratory tract disorder in humans.

2. Combined use of roflumilast and R,R-formoterol in preventing the symptoms of, or treating a respiratory tract disorder in humans, which comprises administering roflumilast in a daily dosage of from 100 to 500 µg and R,R-formoterol in a daily dosage of from 10 to 120 µg.

3. Medicament suited for the combined use according to claim 1 or 2, which comprises roflumilast and R,R-formoterol in fixed or free combination.

4. Medicament according to claim 3, which is a fixed oral combination.

5. Medicament according to claim 3, which is a fixed oral combination containing roflumilast in a daily dosage of from 100 to 500 µg and R,R-formoterol in a daily dosage of from 10 to 120 µg.

6. Medicament according to claim 3, which is a free combination comprising roflumilast in an oral formulation and R,R-formoterol in a formulation suited for administration by inhalation.

7. Medicament according to claim 3, which is a free combination comprising roflumilast in an oral formulation in a daily dosage of from 100 to 500 µg and R,R-formoterol in a formulation suited for administration by inhalation in a daily dosage of from 10 to 50 µg.

8. Medicament according to claim 3, which is a medicament pack containing two pack units with roflumilast in an oral formulation and R,R-formoterol in a formulation suited for administration by inhalation.

9. Method for preventing or reducing the onset of symptoms of a pulmonary disease, or treating or reducing the severity of a pulmonary disease by administering to a patient in need thereof an effective amount of roflumilast and R,R-formoterol either in a single combined form, separately, or separately and sequentially where the sequential administration is close in time, or remote in time.

10. Method according to claim 9, which comprises administering roflumilast in a daily dosage of from 100 to 500 µg and R,R-formoterol in a daily dosage of from 10 to 50 µg.

11. Medicament pack, containing roflumilast as active ingredient, which contains a description that roflumilast can be administered, for reducing the onset of symptoms of a pulmonary disease, or for

treating or reducing the severity of a pulmonary disease, together with R,R-formoterol sequentially, where the sequential administration is close in time, or remote in time in any order whatever.

12. Medicament pack, containing R,R-formoterol as active ingredient, which contains a description that R,R-formoterol can be administered, for reducing the onset of symptoms of a pulmonary disease, or for treating or reducing the severity of a pulmonary disease, together with roflumilast sequentially, where the sequential administration is close in time, or remote in time in any order whatever.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/13266

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/167 A61K31/44 A61P11/00

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

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, EMBASE, WPI Data, PAJ, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	REID P: "ROFLUMILAST" CURRENT OPINION IN INVESTIGATIONAL DRUGS, CURRENT DRUGS, LONDON, GB, vol. 3, no. 8, August 2002 (2002-08), pages 1165-1170, XP001119630 ISSN: 0967-8298	11
Y	page 1165 page 1167, right-hand column, paragraph 4 ---	1-10
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Y	claims 1,7 abstract page 2, last paragraph ---	1-10
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 April 2004	13/04/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Langer, O

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CAMPILLO N ET AL: "Novel bronchodilators in the treatment of asthma and COPD" EXPERT OPINION ON THERAPEUTIC PATENTS 2002 UNITED KINGDOM, vol. 12, no. 1, 2002, pages 53-63, XP002237401 ISSN: 1354-3776	11
A	page 55, right-hand column, line 56 -page 56, right-hand column, paragraph 6 page 58, right-hand column -page 60, left-hand column, paragraph 2 figures 1,4	1-10

X	US 5 795 564 A (MORLEY JOHN ET AL) 18 August 1998 (1998-08-18) column 7, line 1 - line 47	12
Y	abstract claims 1-15 column 1, paragraph 2 - paragraph 3 column 5, line 4 - line 15 column 10, line 53 - line 67	1-10

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Y	WO 02 076933 A (GUNTRIP STEPHEN BARRY ;BIGGADIKE KEITH (GB); FIELD RITA (GB); GLAX) 3 October 2002 (2002-10-03) abstract page 7, line 10 - line 16 page 7, line 23 -page 8, line 2 page 14, line 18 - line 21 page 14, line 23 - line 24 page 16, line 20	1-10

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/13266

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6 288 118 B1 (TORPHY THEODORE J ET AL) 11 September 2001 (2001-09-11) cited in the application claims 1,2 abstract column 4, paragraph 2	1-10
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INTERNATIONAL SEARCH REPORT

International application No.
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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1, 2, 9 and 10 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 03/13266

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