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(54) Title: SYNERGISTIC COMBINATION COMPRISING ROFLUMILAST AND REVATROPATE FOR THE TREATMENT OF RESPIRATORY DISEASES

(57) Abstract: The invention relates to the administration of roflumilast and revatropate, for the treatment of respiratory diseases.

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SYNERGISTIC COMBINATION COMPRISING ROFLUMILAST AND REVATROPATE FOR THE TREATMENT OF RESPIRATORY DISEASES

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 PDE4 inhibitor class and an active compound from the anticholinergic agent class. Their combined use in the sense according to the invention for therapeutic purposes has not jet been described in the prior art.

Prior art

International patent applications WO02/069945 and WO03/011274 generally describe the combination of a compound from the class of PDE4 inhibitors with a compound from the class of anticholinergic agents for the treatment of respiratory tract disorders. International Patent application WO02/096463 describes an inhaled combination of a selective PDE4 inhibitor and an anticholinergic agent, with the proviso that the anticholinergic agent is not a tiotropium salt. International patent application WO02/096423 describes a combination of therapeutic agents useful in the treatment of obstructive airways and other inflammatory diseases comprising (I) a PDE4 inhibitor that is therapeutically effective in the treatment of said diseases when administered by inhalation; together with (II) an anticholinergic agent comprising a member selected from the group consisting of tiotropium and derivatives thereof that is therapeutically effective in the treatment of said diseases when administered by inhalation. In the US patent application No. US2002/0052312 a method for the treatment of chronic obstructive pulmonary disease is described comprising administering orally to a patient in need of such treatment a therapeutically effective amount of a muscarinic receptor antagonist in combination with a therapeutically effective amount of at least one other therapeutic agent selected from the group consisting of: ß2-agonist, antitussive, corticosteroid, decongestant, histamine H1 antagonist, dopamine antagonist, leukotriene antagonist, 5-lipoxygenase inhibitor, phosphodiesterase IV inhibitor, VLA-4 antagonist, and theophylline.

Summary of the invention

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

cally 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 bioavailability
- 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 the anticholinergic agent revatropate outstandingly fulfills the abovementioned conditions, in particular in view of the fact that the combination of the 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 respiratory disease, or treating or reducing the severity of a respiratory disease by administering to a patient in need thereof an effective amount of roflumilast and revatropate.

The invention also relates to a pharmaceutical composition for preventing or reducing the onset of symptoms of a respiratory disease, or treating or reducing the severity of a respiratory disease, comprising an effective amount of roflumilast, an effective amount of revatropate and a pharmaceutical acceptable excipient and/or carrier.

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

The invention furthermore relates to the use of a combination of roflumilast and the anticholinergic agent revatropate for the preparation of a pharmaceutical composition for preventing or reducing the onset of symptoms of a respiratory disease, or treating or reducing the severity of a respiratory disease.

Detailed description of the invention

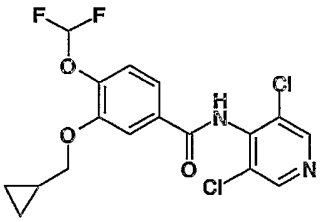
The combination therapy which is the subject matter of this invention comprises administering roflumilast with revatropate to prevent the onset of a respiratory disease event or to treat an existing condition. The two compounds may be administered together in a single dosage form. Or they may be ad-

ministered 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 active compound is administered in the morning and the second active compound is administered in the evening. The combination may be used prophylactic or after the onset of symptoms has occurred. In some instances the combination may be used to prevent the progression of a respiratory disease or to arrest the decline of a function such as lung function.

The invention thus relates to the combined use of roflumilast and revatropate in preventing the symptoms of, or treating a respiratory disease.

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 nonproprietary 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.



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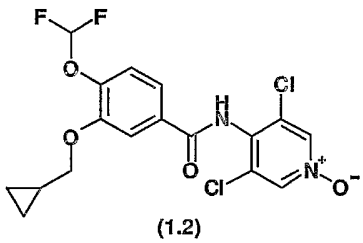
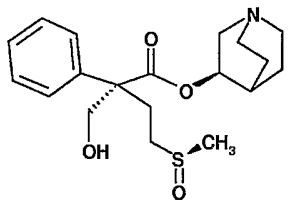


(1.2)

In the sense of the invention, the term "revatropate" is understood to include the pharmaceutically acceptable salts of REVATROPATE, which can likewise be used according to the invention.

REVATROPATE is the international nonproprietary name (INN) for (R)-3-quinuclidinyl-(S)-beta-hydroxy-alpha-[2-(R)-methylsulfinyl]-ethyl]hydratropate [structure of formula (1.3)]. The preparation of (R)-3-quinuclidinyl-(S)-β-hydroxy-α-[2-(R)-methylsulfinyl]-ethyl]hydratropate and its pharmaceutically acceptable salts as well as the use of these compounds as anticholinergic/antimuscarinic agents is described in WO93/06098.



(1.3)

Suitable pharmaceutically acceptable salts of ROFLUMILAST and REVATROPATE 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.

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.

Respiratory diseases 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). The combination is particularly useful in the treatment of COPD.

"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 in succession (from separate pack units –free combination), close in time or remote in time, in any order whatever. As an example, one active compound could be taken in the morning and one later in the day. Or in another scenario, one active compound 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. In case of administration in succession of the two active compounds it is preferred that the anticholinergic agent is administered first and roflumilast thereafter.

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

Roflumilast and revatropate may be administered to a subject in need of treatment by a variety of conventional routes of adminstration, including oral, intranasal or intravenous administration as well as administration by inhalation. This invention contemplates either co-administering both active compounds in one delivery form such as an inhaler, which is putting both active compounds in the same inhaler. Alternatively one can put roflumilast into pills and package them in a medicament pack with an inhaler that contains revatropate. Preferred is the administration of both active compounds in one delivery form, such as a fixed oral combination or – as indicated above – putting both active compounds in the same inhaler.

The selective PDE4 inhibitors and the anticholinergic agents of the present invention may be conveniently delivered in the form of a dry powder inhaler or an aerosol spray presentation from a pressurized container, pump, spray, atomizer (preferably an atomizer using electrodynamics to produce a fine mist) or nebulizer, with or without the use of a suitable propellant, e. g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, a hydrofluoroalkane such as 1,1,2,2-tetrafluoroethane (HFA 134A [trade mark]) or, 1,1,1,2,3,3,3-heptafluoropropane (HFA 227EA [trade mark]), carbon dioxide, a further perfluorinated hydrocarbon such as Perflubon [trade mark] or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered dose. The pressurized container , pump, spray, or nebulizer may contain a solution or suspension of the selective PDE4 inhibitor and/or the anticholinergic agent, e. g. using a mixture of ethanol (optionally aqueous ethanol) or a suitable agent for dispersing, solubilizing or extending release and the propellant as the solvent, which may additionally contain a lubricant, e.g. sorbitan trioleate. Capsules, blisters and cartridges (made, for example, from gelatin or HMPC) for use in an inhaler or insufflator may be formulated to contain a powder mix of the selective PDE4 inhibitor and/or the anticholinergic agent of the invention, a suitable powder base, such as lactose or starch and a performance modifier such as l-leucine, mannitol or magnesium stearate.

Prior to use in a dry powder formulation for inhalation the selective PDE4 inhibitors and the anticholinergic agents of the invention will be micronised to a size suitable for delivery by inhalation (typically considered as less than 5 microns). Micronisation could be achieved by a range of methods, for example spiral jet milling, fluid bed jet milling or use of supercritical fluid crystallization.

A suitable solution formulation for use in an atomizer using electrohydrodynamics to produce a finemist may contain from 1 µg to 10 mg of an anticholinergic agent of the invention and the actuation volume may vary from 1 to 100 µl. A typical formulation may comprise an anticholinergic agent of the invention, propylene glycol, sterile water, ethanol and sodium chloride.

Aerosol or dry powder formulations are preferably arranged so that each metered dose or "puff" contains from 1 to 4000 µg of an anticholinergic agent of the invention for delivery to the patient. The overall daily dose with an aerosol will be in the range from 1 µg to 20 mg which may be administered in a single dose or, alternatively, in divided doses throughout the day.

In case of pharmaceutical compositions which are intended for oral administration, the active ingredients roflumilast and/or revatropate 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, caplets, 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).

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).

Typical formulations for intranasal administration include those mentioned above for inhalation and further include non-pressurized formulations in form of a solution or suspension in an inert vehicle such as water optionally in combination with conventional excipients such as buffers, anti-microbials, tonicity modifying agents and viscosity modifying agents, which may be administered by a nasal pump.

For the above-mentioned prophylactic and therapeutic uses the dosages administered will, of course vary with the first and second active compound employed, the treatment desired and the disorder indicated.

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.

In case of oral administration of (R)-3-quinuclidinyl-(S)-beta-hydroxy-alpha-[2-(R)-methylsulfinyl]-ethyl]-hydratropate (REVATROPATE), the daily dose is likely to range from 0.01 to 1 mg/kg body weight of the subject to be treated, preferably 0.1 to 0.5 mg/kg.

For inhalation, 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloropyrid-4-yl)benzamide (ROFLUMILAST) is administered in a daily dose of 1 to 15 µg/Kg body weight of the subject to be treated, preferably 3 to 7 µg/kg, preferably by once daily administration.

In the case of the oral administration of 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloropyrid-4-yl)benzamide (ROFLUMILAST) the daily dose is in the range 1 to 7 µg/kg body weight of the subject to be treated, preferably by once daily administration.

In the case of the intravenous administration of 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloropyrid-4-yl)benzamide (ROFLUMILAST) the daily dose is in the range from 50 to 500 µg per day, preferably in the range from 150 to 300 µg.

Preparation Examples:

There follows a description of several Examples showing preparation of pharmaceutical compositions containing a combination of active compounds in accordance with the present invention. These examples are intended to further illustrate the combinations of active compounds of the present invention, pharmaceutical compositions containing them and processes in accordance with which said pharmaceutical compositions may be readily prepared by a person skilled in the art. The person skilled in the art will be aware of many other suitable processes and pharmaceutically acceptable carriers that are also available, as well as acceptable variations in the procedures and ingredients described below.

Example 1: Dry Powder Inhaler (mono dose system based on capsule for inhalation)

2.00 g of micronized ROFLUMILAST, 3.20 g of micronized REVATROPATE and 54.8 g of lactose monohydrate are mixed in a turbula mixer in two steps. The blend is screened (0.71 mm sieve) to break up any agglomerates and, subsequently, transferred into the container of a planetary mixer. After adding additional 140.0 g lactose monohydrate and mixing, 25 mg of the blend are filled into hard gelatin capsules size #3 using a capsule filling machine. The capsules can be administered with a commercially available inhaler, e.g., the Cyclohaler®. One capsule contains 250 µg of ROFLUMILAST and 400 µg of REVATROPATE.

Example 2: Dry Powder Inhaler (multi dose system)

6.67 g of micronized ROFLUMILAST and 33.4 g of deagglomerated lactose monohydrate are screened (0.5 mm sieve) and mixed in a turbula mixer until homogenous. 10.67 g of micronized revatropate and 53.4 g of deagglomerated lactose monohydrate are screened (0.5 mm sieve) and mixed in a turbula mixer until homogenous. The ROFLUMILAST and the REVATROPATE pre-blends obtained are screened (0.5 mm sieve) and filled into a stainless steel container together with 295.9 g of deagglomerated lactose monohydrate. The powders are blended in a turbula mixer until homogenous. 1.2 g of the blend are then filled into the reservoir of a multi dose powder inhaler. After fully assembling, the powder inhaler is pouched into a moisture protective aluminum foil.

Such dry powder inhaler may contain 120 individual doses of 7.5 mg powder each containing 125 µg of ROFLUMILAST and 200 µg of REVATROPATE.

Example 3: Roflumilast-Revatropate Tablets

ROFLUMILAST is mixed with corn starch and, subsequently, triturated in a planetary mill. The trituration is screened (1.0 mm sieve) and transferred into the product container of a fluidised bed granulator. REVATROPATE, microcrystalline cellulose and sodium carboxymethylstarch (type A) are added to the product container. A solution of povidone in purified water is sprayed onto the powders under suitable process conditions until granules of a suitable size range are obtained. The granules are dried to the moisture content specified. Magnesium stearate is added to the dried granules using a suitable mixer. The blend is compressed into tablets having an average weight of approx. 80 mg using a standard rotary tablet press. Each tablet contains 250 µg of ROFLUMILAST and 10 mg of REVATROPATE.

Pharmacology

Inhibition of Methacholine-induced Bronchoconstriction in Guinea Pigs by ROFLUMILAST in Combination with REVATROPATE

Objective

To assess the inhibitory effect of REVATROPATE, ROFLUMILAST, and the combination of both compounds on methacholine-induced bronchoconstriction in anaesthetized, mechanically ventilated guinea pigs.

Animals

Male Dunkin Hartley guinea pigs; body weight 350-450 g when performing the experiments.

Experimental procedure

75 min before methacholine-induced bronchospasm (at –75 min) animals were anaesthetized with urethane i.p. (1.2 g/kg). At –55 min for i.v. injections the right jugular vein and for ventilation the trachea was cannulated. At –45 min NaCl 0.9% or REVATROPATE was administered i.v. (1 µg/kg). At -30 min lactose (10 mg/kg) or ROFLUMILAST (4 mg/kg) mixed with lactose was administered intratracheally by a dry powder aerolizer. At –10 min pancuronium-bromide (1.5 mg/kg) was administered i.v. to abolish spontaneous breathing. Animals were mechanically ventilated with 60 breath/min and a tidal volume of 7 ml/kg. Dynamic lung compliance (COM) and airway conductance (CON) were calculated with the help of a computer system from airflow and ventilation pressure signals. At t=0 min methacholine was administered i.v. (60 µg/kg) to induce bronchoconstriction.

Analysis of lung physiology data

COM and CON were determined up to 120 s after methacholine-induced bronchospasm. AUCs for 0 to 120s were determined. Inhibition was calculated based on the AUC data. Data are shown as mean ± SEM. Results were taken to be significant if $p<0.05$ versus placebo (ANOVA and Dunnett's multiple comparison test).

Results

Injection of methacholine induced an immediate bronchoconstriction characterized by a decrease of COM and CON; maximum at 20 s (Fig.1 and Fig. 2).

Pretreatment with ROFLUMILAST had no significant effect on methacholine-induced bronchospasm (Fig. 1 – 4, COM 7.4 %, CON 4.5 %).

Pretreatment with REVATROPATE had no significant effect on methacholine-induced bronchospasm (Fig. 1 – 4, COM 13.5 %, CON –8.4 %).

Combination of both treatments led to an unexpected synergistic significant ($p<0.01$) inhibition of methacholine-induced COM decrease (Fig. 1 and 3, COM 28.5 %) and CON decrease (Fig. 2 and 4, CON 25.8 %, $p<0.05$).

Conclusion

Whereas ROFLUMILAST and REVATROPATE alone had no influence on methacholine-induced bronchospasm in aneasthetized and mechanically ventilated guinea pigs, combination of both active compounds showed an unexpected synergistic inhibition.

Description of the Figures:

Figure 1: Methacholine induced compliance decrease in guinea pigs.

Figure 2: Methacholine induced conductance decrease in guinea pigs.

Figure 3: AUC Compliance 0-120 s

Figure 4: AUC Conductance 0-120 s

Patent claims

1. Combined use of roflumilast and revatropate in preventing the symptoms of, or treating a respiratory disease in humans.

2. Pharmaceutical composition suited for the combined use according to claim 1, which comprises roflumilast and revatropate in fixed or free combination.

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

4. Pharmaceutical composition according to claim 3, which comprises roflumilast in a daily dosage of from 1 to 7 µg/kg and revatropate in a daily dosage of from 0.01 to 1 mg/kg body weight of the subject to be treated.

5. Pharmaceutical composition according to claim 2, which is a free combination comprising roflumilast in an oral formulation and revatropate in a formulation suited for administration by inhalation.

6. Pharmaceutical composition according to claim 2, which is a medicament pack containing two separate pack units, one with roflumilast in an oral formulation and the other with revatropate in a formulation suited for administration by inhalation.

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

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

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

10. Pharmaceutical composition, method or medicament pack according to any of claims 1 to 8, wherein roflumilast represents 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloro-1-oxypyrid-4-yl)benzamide.

11. Pharmaceutical composition, method or medicament pack according to any of claims 1 to 8, wherein revatropate represents (R)-3-quinuclidinyl-(S)-β-hydroxy-α-[2-(R)-methylsulfinyl]-ethyl]hydratropate or the hydrobromide salt thereof.

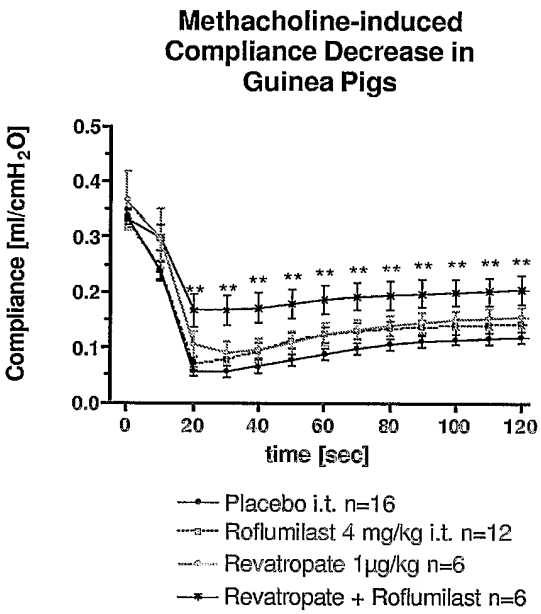
12. Use of a combination of roflumilast and the anticholinergic agent revatropate for the preparation of a pharmaceutical composition for preventing or reducing the onset of symptoms of a respiratory disease, or treating or reducing the severity of a respiratory disease.

13. Use according to claim 12, wherein roflumilast represents 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloropyrid-4-yl)benzamide.

14. Use according to claim 12, wherein roflumilast represents 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloro-1-oxypyrid-4-yl)benzamide.

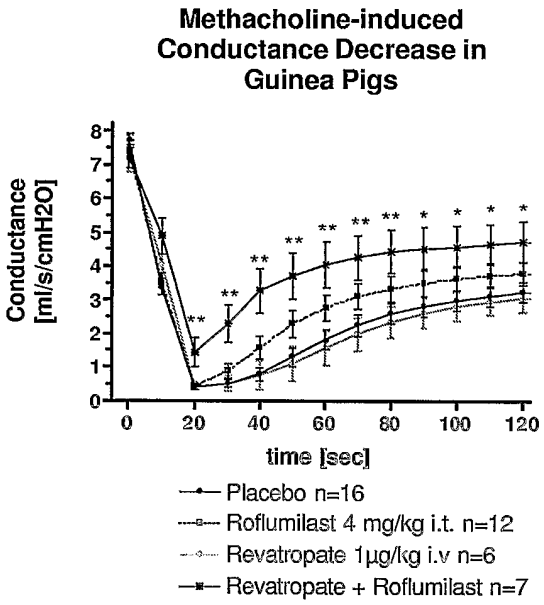
15. Use according to any of claims 12 to 14, wherein revatropate represents (R)-3-quinuclidinyl-(S)-β-hydroxy-α-[2-(R)-methylsulfinyl]-ethyl]hydratropate or the hydrobromide salt thereof.

Figure 1



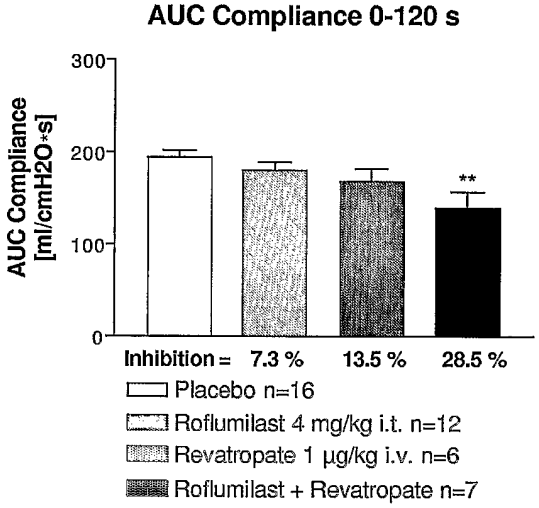
Data are shown as mean ± SEM. **p<0.01 vs. placebo

Figure 2



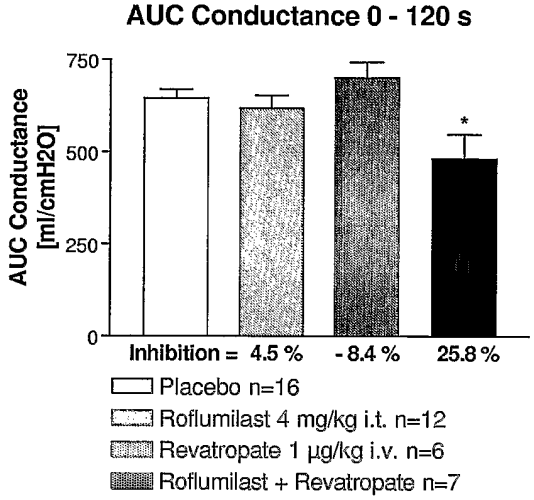
Data are shown as mean ± SEM.*p<0.05, **p<0.01 vs. placebo

Figure 3



Data are shown as mean ± SEM. **p<0.01 vs. placebo.

Figure 4



Data are shown as mean ± SEM. *p<0.05 vs. placebo.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/050374

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/44 A61K31/439

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, WPI Data, PAJ, BIOSIS, MEDLINE, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/069945 A (BOEHRINGER INGELHEIM PHARMA ;PIEPER MICHAEL PAUL (DE); PAIRET MICH) 12 September 2002 (2002-09-12) cited in the application page 1, line 7 - page 3, line 2; page 5, line 9-12	1-15
X	US 2002/052312 A1 (BACH MARK A ET AL) 2 May 2002 (2002-05-02) '0006!; '0009!-'0011!; '0024!; '0037!	1-15

-/--

[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
18 August 2004	01/09/2004

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	Borst, M

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/050374

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	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 page 1168: paragraph entitled "Current Opinion"	1-15
Y	ALABASTER V A: "DISCOVERY & DEVELOPMENT OF SELECTIVE M3 ANTAGONISTS FOR CLINICAL USE" LIFE SCIENCES, PERGAMON PRESS, OXFORD, GB, vol. 60, no. 13/14, 1997, pages 1053-1060, XP001056370 ISSN: 0024-3205 page 1054-1057: paragraph entitled "Revatropate: - a drug for treatment of COAD"	1-15
A	CAMPILLO N ET AL: "NOVEL BRONCHODILATORS IN THE TREATMENT OF ASTHMA AND COPD" EXPERT OPINION ON THERAPEUTIC PATENTS, ASHLEY PUBLICATIONS, GB, vol. 1, no. 12, 2002, pages 53-63, XP008002080 ISSN: 1354-3776 page 58-60, paragraph entitled "5. Phosphodiesterase 4 inhibitors"	1-15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2004/050374

Box II Observations where certain claims were found unsearchable (Continuation of item 2 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:

see FURTHER INFORMATION sheet PCT/ISA/210

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 III Observations where unity of invention is lacking (Continuation of item 3 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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Claims Nos.: -

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy:
Although independent claims 1, 8 and dependent claims 9-11 insofar as they relate to said independent claims are directed to a method of treatment of the human body, the search has been carried out and based on the alleged effects of the compound/composition.
Rule 39.1(v) PCT - Presentation of information
Although independent claim 8 and dependent claims 9-11 insofar as they relate to independent claim 8 try to gain protection for the mere presentation of information, the search has been carried out and based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2004/050374

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 02069945 A	12-09-2002	DE 10110772 A1	12-09-2002
		CA 2439763 A1	12-09-2002
		WO 02069945 A2	12-09-2002
		EP 1372649 A2	02-01-2004
		HU 0400782 A2	28-07-2004
		JP 2004521134 T	15-07-2004
		US 2002193393 A1	19-12-2002
		US 2004024007 A1	05-02-2004
US 2002052312 A1	02-05-2002	NONE	