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

(19) World Intellectual Property Organization
International Bureau

(43) International publication date
19 August 2004 (19.08.2004)

PCT

(10) International publication number
WO 2004/069253 A1

(51) International patent classification[7]: A61K 31/496, 9/14, A61P 31/04

(21) International application number: PCT/EP2004/000710

(22) International filing date: 28 January 2004 (28.01.2004)

(25) Language of filing: German

(26) Language of publication: German

(30) Data relating to the priority:
103 05 319.0 10 February 2003 (10.02.2003) DE
103 05 318.2 10 February 2003 (10.02.2003) DE

(71) Applicant *(for all designated States except US)*: BAYER HEALTHCARE AG [DE/DE]; 51368 Leverkusen (DE).

(74) Inventors; and
(75) Inventors/Applicants *(US only)*: ENDERMANN, Rainer [DE/DE]; In den Birken 152A, 42113 Wuppertal (DE). LABISCHINSKI, Harald [DE/DE]; Katernberger Schulweg 80, 42113 Wuppertal (DE). LADEL, Christoph [DE/DE]; In den Birken 28, 42113 Wuppertal (DE). PETERSEN, Uwe [DE/DE]; Auf dem Forst 4, 51375 Leverkusen (DE). NEWTON, Ben [GB/GB]; Wyburn, 44 Bois Lane, Chesham Bois, Amersham, Buckinghamshire HP6 6BX (GB).

(74) Joint Representative: BAYER HEALTHCARE AG; Law and Patents, Patents and Licensing, 51368 Leverkusen (DE).

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

(84) Designated states *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, 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, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
- *With the International Search Report.*

For an explanation of the two-letter codes and the other abbreviations, reference is made to the explanations ("Guidance Notes on Codes and Abbreviations") at the beginning of each regular edition of the PCT Gazette.

As printed

WO 2004/069253 A1

(54) Title: TREATMENT OF BACTERIAL DISEASES OF THE RESPIRATORY ORGANS BY LOCALLY APPLYING FLUOROQUINOLONES

(54) Bezeichnung: BEHANDLUNG BAKTERIELLER ERKRANKUNGEN DER ATMUNGSORGANE DURCH LOKALE APPLIKATION VON FLUORCHINOLONEN

(57) Abstract: The invention relates to inhalable quinolone carboxylic acid derivative compositions for locally combating diseases of the respiratory organs, especially lung diseases.

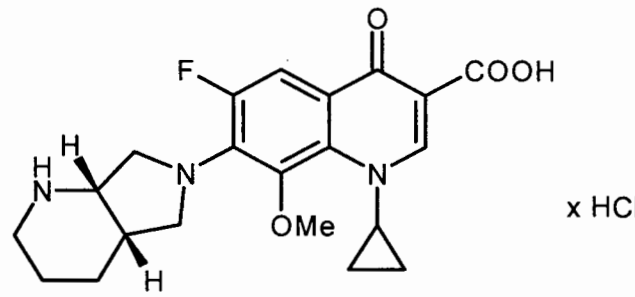
(57) Zusammenfassung: Die Erfindung betrifft inhalierbare Chinoloncarbonsäurederivat-Zusammensetzungen zur lokalen Bekämpfung von Erkrankungen der Atmungsorgane, insbesondere von Lungenkrankheiten.

TREATMENT OF BACTERIAL DISEASES OF THE RESPIRATORY ORGANS BY LOCALLY APPLYING FLUOROQUINOLONES

The present invention relates to the use of dosage forms which contain quinolonecarboxylic acid derivatives and enable local treatment of diseases of the respiratory organs, in particular lung diseases caused by bacteria.

Despite enormous progress in the area of controlling bacterial infectious diseases through the introduction of various classes of antibiotics in the last 70 years, severe lung infections still represent an important problem, especially in relation to pathological states such as cystic fibrosis, bronchiectasis and increasingly also chronic obstructive pulmonary diseases (COPD), which are associated with infections which can be treated only with difficulty or not at all. Active ingredients from the class of fluoroquinolones, especially also moxifloxacin and ciprofloxacin, are frequently employed for the treatment of such diseases because of their relevant range of antibacterial effects and their bactericidal action.

Moxifloxacin hydrochloride (I)



(I)

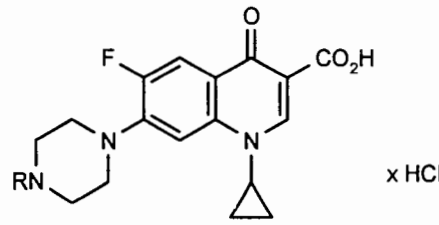
is an antibacterial active ingredient from the class of quinolonecarboxylic acid derivatives for the treatment and prevention of otitis, pharyngitis, pneumonia, peritonitis, pyelonephritis, cystitis, endocarditis, systemic infections, acute and chronic bronchitis, septic infections, diseases of the upper airways, diffuse panbronchiolitis, pulmonary emphysema, dysentery, enteritis, liver abscesses, urethritis, prostatitis, epididymitis, gastrointestinal infections, bone and joint infections, cystic fibrosis, skin infections, postoperative wound infections, abscesses, phlegmons, wound infections, infected burns, burns, infections in the oral region, infections after dental operations, osteomyelitis, septic arthritis, cholecystitis, peritonitis with appendicitis, cholangitis, intraabdominal abscesses, pancreatitis, sinusitis, mastoiditis, mastitis, tonsillitis, typhoid, meningitis, infections of the nervous system, salpingitis, endometritis, genital infections, pelveoperitonitis and eye infections (EP 350 733 B1, US 4 990 517, 5 607 942 and WO 01/45679).

The principal indications for moxifloxacin are diseases of the respiratory tract, especially of the lungs.

Dosage forms for moxifloxacin mentioned in EP-B 350 733 are tablets, coated tablets, capsules, pills, granules, suppositories, solutions, suspensions and emulsions, pastes, ointments, gels, creams, lotions, dusting powders and sprays. To our knowledge, only tablets and (for intravenous administration) solutions are on the market.

In practice, moxifloxacin has to date been used exclusively systemically for all diseases for the control of which it is suitable (including those of the lungs). The reason for this is the high oral bioavailability and the good distribution of the active ingredient. Although the increase in the active ingredient concentration in the serum and lungs of rats after local (intratracheal) administration of moxifloxacin hydrochlroride is greater than with systemic (oral) administration of the same amount of moxifloxacin hydrochloride, its concentration also falls relatively rapidly (within about an hour) to the level of the concentration reached orally, so that intratracheal local administration achieves no advantages compared with oral administration in experiments on rats too.

Ciprofloxacin hydrochloride and enrofloxacin hydrochloride (II) are antibacterial quinolonecarboxylic acid derivatives which have been known for about 20 years (EP-B 49 355, US-A 4 670 444) and which can be employed extremely successfully both for the prophylaxis and for the treatment of systemic and local bacterial infections, especially of the urinary tract. Ciprofloxacin is also effective inter alia against anthrax pathogens.



(II)

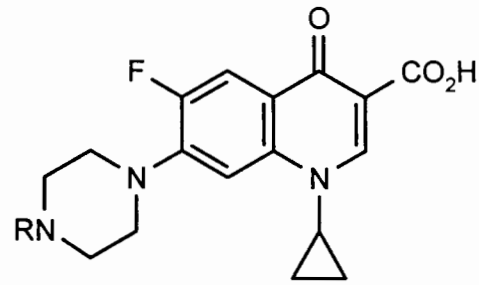
ciprofloxacin hydrochloride: R = H
enrofloxacin hydrochloride: R = C_2H_5

The dosage forms of ciprofloxacin/enrofloxacin mentioned in EP-B 49 355 are tablets, coated tablets, capsules, pills, granules, suppositories, solutions, suspensions and emulsions, pastes, ointments, gels, creams, lotions, dusting powders and sprays. Ciprofloxacin tablets, suspensions, eye and ear drops and solutions suitable for intravenous infusion are currently on the market.

It has been found, surprisingly, that control of diseases of the respiratory organs, especially lung diseases caused by bacteria, is extremely successful when ciprofloxacin or enrofloxacin is administered locally as solid betaine and/or as solid slightly soluble betaine salt. The active

ingredient concentration in the lungs can be kept for a lengthy period at a level desirable from the medical viewpoint for optimal treatment. Besides the higher and long-lasting active ingredient level at the site of the infection, it is possible to achieve simultaneously a comparatively low systemic concentration of the active ingredient, so that side effects of the medication and the disquieting development of resistance through systemic selection pressure are at least drastically reduced or even entirely prevented in this way.

The invention therefore relates to a method for controlling diseases of the respiratory organs, especially lung diseases caused by bacteria, in humans and animals by local administration of an antibacterially effective amount of solid betaine of the formula (III)



(III)

R = H, C_2H_5

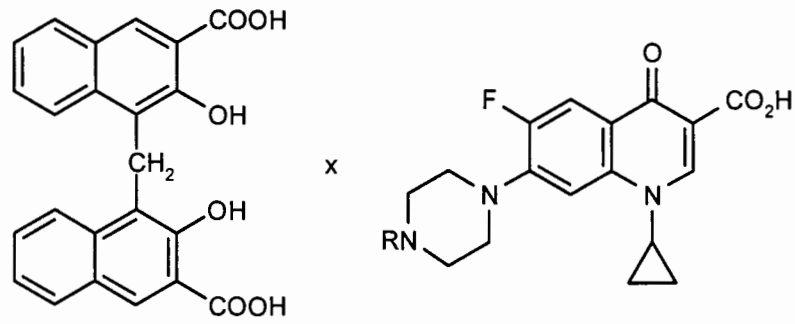
and/or of its solid slightly soluble salt and to the use of these compounds for producing medicaments for the local control of diseases of the respiratory organs, especially lung diseases caused by bacteria, in humans and animals, where the compounds are administered in solid form.

"Slightly soluble salts" for the purposes of the invention have a solubility in water of less than 0.1, preferably less than 0.01, % by weight based on water at 25°C and a pH of 7. Such slightly soluble salts include C_{16}-C_{18} fatty acid salts of the betaine (III) and salts of the betaine (III) with acids such as, for example, the embonates or else salts of the betaine (III) with bases such as N,N'-dibenzylethylenediamine.

The invention relates in a preferred embodiment to a method for controlling diseases of the respiratory organs, especially lung diseases caused by bacteria, in humans and animals by local administration of an antibacterially effective amount of solid betaine of the formula (III) and/or its embonate and to the use of these compounds for producing medicaments for the local control of diseases of the respiratory organs, especially lung diseases caused by bacteria, in humans and animals, where the compounds are administered in solid form.

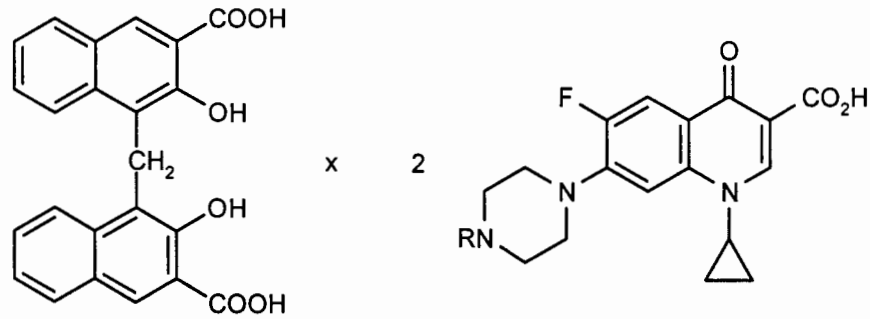
In a particular embodiment of the invention, the diseases of the respiratory organs comprise diseases, caused by bacteria, of the airways or of the lungs, especially lung dieases caused by bacteria.

The embonates (also called pamoates) are salts of embonic acid, corresponding to formula (IV a) and/or (IV b):



(IV a)

R = H, C_2H_5



(IV b)

The term "embonate" refers for the purposes of the invention to the embonate, the hemiembonate and to mixtures thereof.

The term "respiratory organs" (or respiratory system) refers for the purposes of the invention to the nose, oral cavity and pharynx, and the larynx, trachea and lungs, including the airways and the paranasal sinuses and frontal sinus, where "airways" (or respiratory tract) mean the nasal cavity, oral cavity, pharynx, larynx, trachea and bronchi.

"Local administration" or "local control" in connection with diseases of the respiratory organs, especially lung diseases, means for the purposes of the invention - in contrast to oral administration of dosage forms intended for absorption via the gastrointestinal tract, and in contrast to intravenous administration - administration of the active ingredient by inhalation in inhalable dosage form. The preparation in powder form or powder-containing suspensions to be used according to the invention are preparations which are aerosolized and then inhaled.

The term "inhalation" or "administration by inhalation" refers in this connection to the introduction into the respiratory organs, especially into and/or via the airways, preferably into and/or via the nasal cavity and oral cavity.

The term "intratracheal" or "intratracheal administration" refers for the purposes of the invention to introduction into the trachea not by inhalation, in particular for pulmonary disease control in experimental animals such as rats as a model of administration by inhalation.

The invention further relates to devices which contain preparations containing betaine (III) and/or its solid slightly soluble salt, in particular its embonate, and which are suitable for the administration by inhalation thereof in solid form, i.e. aerosolizers which are able to administer preparations containing betaine (III) and/or its solid slightly soluble salt, in particular its embonate, by inhalation in solid form (powder inhalers), or aersolizers which are able to administer suspensions containing betaine (III) and/or its solid slightly soluble salt, in particular its embonate, in solid form by inhalation (suspension sprays).

Solid preparations for dry powder inhalation or suspension inhalation will generally contain an amount of active ingredient (i.e. betaine (III) and/or its solid slightly soluble salt, in particular its embonate) which is as high as possible. The amount of active ingredient therein is usually at least 60, preferably at least 70, in particular at least 80 and most preferably at least 90, % by weight based on the preparation ready for use. However, the amount of active ingredient therein may also be less than 60% by weight based on the preparation ready for use and is then preferably at least 30, in particular at least 40, % by weight based on the preparation ready for use. Where no adjuvants are necessary, especially in the case of solid preparations for suspension inhalation, they may also consist of active ingredient alone. However, for practical reasons, the preparations according to the invention are often medicaments which, besides the active ingredient, contain one or more pharmacologically acceptable excipients. A review of various suitable preparations and corresponding administration aids is to be found for example in R. Stangl, "An Overview of Innovative Inhalation Devices", European Pharmaceutical Review, pages 50-55, (2002) and the literature cited therein. Pharmacologically acceptable excipients include, inter alia, binders (e.g. maize starch, gelatin), stabilizers (e.g. antioxidants such as ascorbic acid), carriers (e.g. microcrystalline cellulose, lactose, sucrose, calcium phosphate, maize starch), lubricants (e.g. talc, stearic acid, magnesium stearate, calcium stearate or zinc stearate), flavourings and/or fragrances. The production of suitable preparations by selecting suitable excipients in terms of nature and quantity is straightforward.

The preparations according to the invention can be produced - as is usual in the production of inhalable free-flowing medicaments in powder form, by micronizing the active ingredient or by spray drying appropriate solutions or suspensions.

The solid preparations generally have a particle diameter, determined as volume median (with the aid of a laser diffraction apparatus), of from 0.2 to 15 μm, preferably from 1 to 5 μm. The diameter

determined as volume median is the value below and above which 50% of the volume of the particles lie.

In a preferred embodiment, the solid preparations have particle diameters, determined as 50% of volume median, of from 2 to 5 µm and particle diameters, determined as 90% volume proportion, of from 6 to 10 µm. In a further preferred embodiment, the solid preparations contain active ingredient, in particular ciprofloxacin betaine, with a particle diameter, determined as 50% volume median, of from 2 to 5 µm and particle diameters, determined as 90% volume proportion, of from 6 to 10 µm. The diameter determined as 50% or 90% volume proportion (with the aid of a laser diffraction apparatus) is the value below which respectively 50% and 90% of the volume of the particles lie. Thus, for example, in a solid preparation with a particle diameter, determined as 50% volume median, of 2 µm and a particle diameter, determined as 90% volume proportion, of 6 µm (50% < 2 µm; 90% < 6 µm) the particle diameter of 50% of the volume of the particles is below 2 µm and of 90% of the volume of the particles is below 6 µm.

It has generally proved advantageous in administration by inhalation to administer amounts of about 0.1 to 20, preferably about 0.5 to 7.5, mg/kg of bodyweight to achieve effective results.

It may nevertheless be necessary to depart from the stated amounts, specifically as a function of the bodyweight, individual behaviour towards the active ingredient, nature of the preparation and time or interval over which administration takes place. Thus, it may suffice in some cases to make do with less than the aforementioned minimum amount, whereas in other cases the said upper limit must be exceeded. Where larger amounts are administered, it may be advisable to divide them into a plurality of single doses over the day.

Examples

Preparation of ciprofloxacin embonate

a) Ciprofloxacin embonate (IV a; R = H)

33.1 g (0.1 mol) of ciprofloxacin betaine and 38.8 g (0.1 mol) of embonic acid are heated in 500 ml of glycol monomethyl ether under reflux for 1 hour. After cooling, the precipitate is filtered off with suction, thoroughly washed with ethanol and dried at 120°C under high vacuum.

b) Ciprofloxacin hemiembonate (IV b; R = H)

66.2 g (0.2 mol) of ciprofloxacin betaine and 38.8 g (0.1 mol) of embonic acid are heated in 500 ml of glycol monomethyl ether under reflux for 1 hour. After cooling, the precipitate is filtered off with suction, thoroughly washed with ethanol and dried at 120°C under high vacuum.

Determination of the active ingredient concentration in the lungs of rats

Female Wistar rats (80 to 100 g) were treated with

A1 - 7.5 mg/kg ciprofloxacin betaine (laboratory product) intratracheally as suspension;

A2 - 7.5 mg/kg ciprofloxacin betaine (micronized: 50% < 3 µm; 90% < 7 µm) intratracheally as suspension;

B - 7.5 mg/kg ciprofloxacin hydrochloride intratracheally as solution;

C - 7.5 mg/kg ciprofloxacin-hydrochloride intravenously as solution.

Three animals from each of the dose groups were sacrificed after 0.25, 0.5, 1, 3 and 5 hours, and the lungs were removed. The lungs were homogenized using a Plotter from Braun. The active ingredient content in the lung homogenates was determined by bioassay.

Pharmacokinetic parameters for the lungs

Dose group	AUC [mg*h/l]	C_{max} [mg/l]	$t_{1/2}$ [h]
A1	124	49.1	1.96
A2	304	76	13.47
B	3.20	6.65	0.847
C	0.497	0.610	0.758

Lung concentrations in µg/ml; averages for 3 animals

Dose group	0.25 h	0.5 h	1 h	3 h	5 h
A1	49.1	44.3	40.1	12.6	7.21
A2	76	76	76	54	54
B	6.65	1.67	0.63	0.10	0
C	0.61	0.35	0.14	0	0

AUC, C_{max} and $t_{1/2}$ are important pharmacokinetic parameters for describing pharmacokinetic/pharmacodynamic interactions; cf., for example, W.A. Craig, "Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men", Clin. Infect. Dis. 26, 1-12 (1998).

Intratracheal administration of ciprofloxacin-betaine (laboratory product) reveals, compared with intratracheal administration of ciprofloxacin-hydrochloride, a 40 times larger AUC and an 8 times higher C_{max}. This kinetic advantage becomes even clearer on comparison with intravenous administration of ciprofloxacin hydrochloride (AUC: factor 250, C_{max}: factor 80). Intratracheal administration of micronized ciprofloxacin-betaine with a particle diameter (50 % < 3 µm; 90 % < 7 µm) leads to a further improvement in the pharmacokinetic profile (AUC: factor 612, C_{max}: factor 125, compared with intravenous administration of ciprofloxacin hydrochloride).

Efficacy in a model of lung infection with P. aeruginosa

Female Wistar rats (80 to 100 g) were infected intratracheally with P. aeruginosa DSM 12055 and treated 1 and 4 hours after the infection with ciprofloxacin betaine (laboratory product) intratracheally (i.t.) and with ciprofloxacin hydrochloride intratracheally and intravenously (i.v.). Various dose groups each of 5 rats were employed. The animals were sacrificed 24 hours after the infection, and the lungs were removed and homogenized with a Potter from Braun. The homogenates were plated out to determine the microbe count in the lungs.

The following table shows the **reduction in the microbe count in the lungs** (log units) after 24 h relative to the untreated infection control (in each case averages for 5 animals):

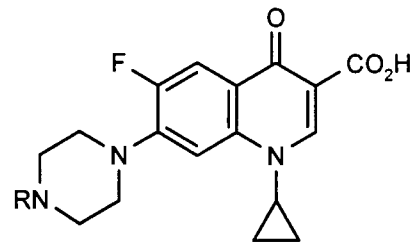
Dose group	Reduction in microbe count (log units)
A - 0.8 mg/kg ciprofloxacin betaine i.t.	-4.0
B - 2.5 mg/kg ciprofloxacin betaine i.t.	-5.8
C - 7.5 mg/kg ciprofloxacin betaine i.t.	-10
D - 0.8 mg/kg ciprofloxacin hydrochloride i.t.	-1.8
E - 2.5 mg/kg ciprofloxacin hydrochloride i.t.	-1.1
F - 7.5 mg/kg ciprofloxacin hydrochloride i.t.	-2.8
G - 2.5 mg/kg ciprofloxacin hydrochloride i.v.	-2.8
H - 7.5 mg/kg ciprofloxacin hydrochloride i.v.	-3.5
I - 22.5 mg/kg ciprofloxacin hydrochloride i.v.	-5.4
J - 67.5 mg/kg ciprofloxacin hydrochloride i.v.	-8.8

Intratracheal use of ciprofloxacin betaine leads to a reduction of from 4 to 10 log units in the microbe count in the lungs in all three dose groups, whereas equal dosages of ciprofloxacin hydrochloride administered intratracheally bring about a far smaller reduction in the microbe count (1.1 to 2.8 log units). Although intravenous administration of ciprofloxacin hydrochloride, the current state of the art, also leads to a marked reduction in the microbe count in the lungs (2.8 to 8.8 log units), this is only with dosages which are 10 times higher. The treatment according to the invention thus leads to a greatly reduced systemic exposure.

In a further test with P.aeruginosa DSM 12055, a single intratracheal treatment (1 hour after the infection) was carried out with micronized ciprofloxacin betaine as dry powder. A dose of 10 mg/kg was administered with the aid of a DP-3 dry powder insufflator (PENN-CENTURY, INC.). It is known from control investigations that about 5 to 20% of the administered dose reach the lungs. In this experiment, the microbe count in the lungs was reduced by more than 6 log units compared with an untreated control group.

Patent claims

1. Method for controlling bacterial diseases of the respiratory organs in humans and animals by local administration of an antibacterially effective amount of solid betaine of the formula (III)



(III)

R = H, C_2H_5

and/or its solid slightly soluble salt.

2. Method according to Claim 1 for controlling lung diseases caused by bacteria.

3. Method according to Claim 1 or 2 by local administration of an antibacterially effective amount of solid betaine of the formula (III) according to Claim 1 and/or its embonate.

4. Use of the compounds defined in Claim 1 or 3 for producing medicaments for the local control of bacterial diseases of the respiratory organs in humans and animals, where these compounds are administered in solid form.

5. Use according to Claim 4 for producing medicaments for the local control of lung diseases caused by bacteria.

6. Devices suitable for administration by inhalation of solid active ingredient and containing preparations with at least one of the compounds defined in Claim 1 or 3.

7. Devices according to Claim 6, designed as powder inhalers.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2004/000710

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:

see supplemental 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 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 application No.
PCT/EP2004/000710

Continuation of Box II, 1

PCT Rule 39.1(iv) – Method for treatment of the human or animal body by therapy.
Although claims 1 to 5 relate to a method for treatment of the human or animal body, the search was carried out and was based on the stated effects of the compound or composition.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/000710

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/496 A61K9/14 A61P31/04

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, 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 01/32144 A (INHALE THERAPEUTIC SYST ; LECHUGA BALLESTEROS DAVID (US); KUO MEI CHAN) 10 May 2001 (2001-05-10) Seite 1, Zeile 11-17; Seite 6, Zeile 7-11; Seite 10, Zeile 30 - Seite 11, Zeile 2; Seite 24, Zeile 24	1-7
X	EP 0 504 112 A (CIBA GEIGY AG ; JAGO PHARMA AG (CH)) 16 September 1992 (1992-09-16) Seite 4, Zeile 23-31, 43-44	1-3,6
P,X	WO 03/090715 A (FEELEY JANE CATHERINE ; REHMAN MAHBOOB UR (GB); YORK PETER (GB); NEKTA) 6 November 2003 (2003-11-06) Seite 22, Zeile 28; Anpruch 1	1-7

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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
21 May 2004	14 07 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/EP2004/000710

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 209 000 A (BAYER AG) 21 January 1987 (1987-01-21) the whole document -----	1-7

INTERNATIONALER RECHERCHENBERICHT

Angaben zu Veröffentlichungen, die zur selben Patentfamilie gehören

internat... Aktenzeichen
PCT/EP2004/000710

Im Recherchenbericht angeführtes Patentdokument	Datum der Veröffentlichung	Mitglied(er) der Patentfamilie		Datum der Veröffentlichung
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INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen
PCT/EP2004/000710

Feld II Bemerkungen zu den Ansprüchen, die sich als nicht recherchierbar erwiesen haben (Fortsetzung von Punkt 2 auf Blatt 1)

Gemäß Artikel 17(2)a) wurde aus folgenden Gründen für bestimmte Ansprüche kein Recherchenbericht erstellt:

1. [X] Ansprüche Nr. -
weil sie sich auf Gegenstände beziehen, zu deren Recherche die Behörde nicht verpflichtet ist, nämlich

siehe BEIBLATT PCT/ISA/210

2. [ ] Ansprüche Nr.
weil sie sich auf Teile der internationalen Anmeldung beziehen, die den vorgeschriebenen Anforderungen so wenig entsprechen, daß eine sinnvolle internationale Recherche nicht durchgeführt werden kann, nämlich

3. [ ] Ansprüche Nr.
weil es sich dabei um abhängige Ansprüche handelt, die nicht entsprechend Satz 2 und 3 der Regel 6.4 a) abgefaßt sind.

Feld III Bemerkungen bei mangelnder Einheitlichkeit der Erfindung (Fortsetzung von Punkt 3 auf Blatt 1)

Die internationale Recherchenbehörde hat festgestellt, daß diese internationale Anmeldung mehrere Erfindungen enthält:

1. [ ] Da der Anmelder alle erforderlichen zusätzlichen Recherchengebühren rechtzeitig entrichtet hat, erstreckt sich dieser internationale Recherchenbericht auf alle recherchierbaren Ansprüche.

2. [ ] Da für alle recherchierbaren Ansprüche die Recherche ohne einen Arbeitsaufwand durchgeführt werden konnte, der eine zusätzliche Recherchengebühr gerechtfertigt hätte, hat die Behörde nicht zur Zahlung einer solchen Gebühr aufgefordert.

3. [ ] Da der Anmelder nur einige der erforderlichen zusätzlichen Recherchengebühren rechtzeitig entrichtet hat, erstreckt sich dieser internationale Recherchenbericht nur auf die Ansprüche, für die Gebühren entrichtet worden sind, nämlich auf die Ansprüche Nr.

4. [ ] Der Anmelder hat die erforderlichen zusätzlichen Recherchengebühren nicht rechtzeitig entrichtet. Der internationale Recherchenbericht beschränkt sich daher auf die in den Ansprüchen zuerst erwähnte Erfindung; diese ist in folgenden Ansprüchen erfaßt:

Bemerkungen hinsichtlich eines Widerspruchs

[ ] Die zusätzlichen Gebühren wurden vom Anmelder unter Widerspruch gezahlt.

[ ] Die Zahlung zusätzlicher Recherchengebühren erfolgte ohne Widerspruch.

WEITERE ANGABEN PCT/ISA/ 210

Fortsetzung von Feld II.1

Ansprüche Nr.: -

Regel 39.1(iv) PCT - Verfahren zur therapeutischen Behandlung des menschlichen oder tierischen Körpers:
Obwohl die Ansprüche 1-5 sich auf ein Verfahren zur Behandlung des menschlichen/tierischen Körpers beziehen, wurde die Recherche durchgeführt und gründete sich auf die angeführten Wirkungen der Verbindung/Zusammensetzung.

INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen
PCT/EP2004/000710

A. KLASSIFIZIERUNG DES ANMELDUNGSGEGENSTANDES
IPK 7 A61K31/496 A61K9/14 A61P31/04

Nach der Internationalen Patentklassifikation (IPK) oder nach der nationalen Klassifikation und der IPK

B. RECHERCHIERTE GEBIETE

Recherchierter Mindestprüfstoff (Klassifikationssystem und Klassifikationssymbole)
IPK 7 A61K A61P

Recherchierte aber nicht zum Mindestprüfstoff gehörende Veröffentlichungen, soweit diese unter die recherchierten Gebiete fallen

Während der internationalen Recherche konsultierte elektronische Datenbank (Name der Datenbank und evtl. verwendete Suchbegriffe)
EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE, EMBASE, CHEM ABS Data

C. ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie°	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
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[X] Weitere Veröffentlichungen sind der Fortsetzung von Feld C zu entnehmen

[X] Siehe Anhang Patentfamilie

° Besondere Kategorien von angegebenen Veröffentlichungen :
"A" Veröffentlichung, die den allgemeinen Stand der Technik definiert, aber nicht als besonders bedeutsam anzusehen ist
"E" älteres Dokument, das jedoch erst am oder nach dem internationalen Anmeldedatum veröffentlicht worden ist
"L" Veröffentlichung, die geeignet ist, einen Prioritätsanspruch zweifelhaft erscheinen zu lassen, oder durch die das Veröffentlichungsdatum einer anderen im Recherchenbericht genannten Veröffentlichung belegt werden soll oder die aus einem anderen besonderen Grund angegeben ist (wie ausgeführt)
"O" Veröffentlichung, die sich auf eine mündliche Offenbarung, eine Benutzung, eine Ausstellung oder andere Maßnahmen bezieht
"P" Veröffentlichung, die vor dem internationalen Anmeldedatum, aber nach dem beanspruchten Prioritätsdatum veröffentlicht worden ist
"T" Spätere Veröffentlichung, die nach dem internationalen Anmeldedatum oder dem Prioritätsdatum veröffentlicht worden ist und mit der Anmeldung nicht kollidiert, sondern nur zum Verständnis des der Erfindung zugrundeliegenden Prinzips oder der ihr zugrundeliegenden Theorie angegeben ist
"X" Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann allein aufgrund dieser Veröffentlichung nicht als neu oder auf erfinderischer Tätigkeit beruhend betrachtet werden
"Y" Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann nicht als auf erfinderischer Tätigkeit beruhend betrachtet werden, wenn die Veröffentlichung mit einer oder mehreren anderen Veröffentlichungen dieser Kategorie in Verbindung gebracht wird und diese Verbindung für einen Fachmann naheliegend ist
"&" Veröffentlichung, die Mitglied derselben Patentfamilie ist

Datum des Abschlusses der internationalen Recherche	Absendedatum des internationalen Recherchenberichts
21. Mai 2004	04. 07. 2004

Name und Postanschrift der Internationalen Recherchenbehörde	Bevollmächtigter Bediensteter
Europäisches Patentamt, 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

C.(Fortsetzung) ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie*	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
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