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(54) Benævnelse: INHALATIONSSAMMENHÆNDE INDEHOLDENDE Aclidinium TIL BEHANDLING AF ASTMA

(56) Fremdragne publikationer:

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DESCRIPTION

[0001] This invention relates to a novel dosage for aclidinium and to novel methods and formulations for the treatment of asthma using aclidinium.

BACKGROUND


[0004] Although aclidinium bromide is known to be a long-acting anticholinergic useful in the treatment of respiratory diseases, the optimal dosage is not disclosed.

SUMMARY OF THE INVENTION

[0005] It is now surprisingly found that, for treatment of asthma, in an adult human, aclidinium is most effective upon administration by inhalation in a dosage of 200 micrograms (plus/minus 10%) per metered nominal dose, typically a single dosage of 200 micrograms (plus/minus 10%) per day metered nominal dose (weight corresponding to aclidinium bromide).

[0006] The invention thus provides in a first embodiment a pharmaceutical composition comprising aclidinium in the form of a dry powder of a pharmaceutically acceptable salt in admixture with a pharmaceutically acceptable dry powder carrier, providing a metered nominal dose of aclidinium equivalent to 200 micrograms (plus/minus 10%) aclidinium bromide for use by inhalation in the treatment of asthma.

[0007] The pharmaceutical composition for inhalation comprising aclidinium in the form of a dry powder of a pharmaceutically acceptable salt, e.g., aclidinium bromide, in admixture with a pharmaceutically acceptable dry powder carrier, e.g., lactose particles. The composition may be in the form of (i) a single metered nominal dose of aclidinium equivalent to 200 (plus/minus 10%) micrograms aclidinium bromide, or (ii) a multidose dry powder inhaler device calibrated to provide a metered nominal dose of aclidinium equivalent to 200 micrograms (plus/minus 10%) aclidinium bromide. This composition can be administered one or more times per day. Preferably once or twice a day.

[0008] Also described herein is a method of treating asthma in a patient in need of such treatment, comprising administering a dose, typically a single daily dose or twice daily dose, of aclidinium, e.g., aclidinium bromide, equivalent to 200 micrograms (plus/minus 10%) metered nominal dose aclidinium bromide, e.g., comprising administering a pharmaceutical composition as described above. Also described is the use of aclidinium in the manufacture of a medicament, e.g., as described above, for use in such a method.

[0009] The aclidinium may be administered as monotherapy, or in combination with one or more additional anti-inflammatory and/or bronchodilating agents, e.g., corticosteroids, PDE IV inhibitors and β2-agonists, e.g., formoterol, salmeterol, budesonide, and mometasone, and the invention thus further provides methods as described above further comprising administration of an effective amount of such an agent, as well as pharmaceutical compositions as described above, further comprising such additional agent(s).

DETAILED DESCRIPTION OF THE INVENTION

[0010] Typically, the aclidinium is administered in the form of a salt with an anion X wherein X is a pharmaceutically acceptable anion of a mono or polyvalent acid. More typically, X is an anion derived from an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulphuric acid and phosphoric acid, or an organic acid such as methanesulphonic acid, acetic acid, fumaric acid, succinic acid, lactic acid, citric acid or maleic acid. Preferably the aclidinium is in the form of aclidinium bromide.
[0011] The acilidium is administered in the form of a dry powder, in admixture with a suitable carrier, e.g., lactose powder, suitable for inhalation.

[0012] For example, in one embodiment, the acilidium is acilidium bromide in admixture with lactose powder.

[0013] The respiratory disease or condition to be treated with the formulations and methods described herein is asthma.

[0014] The emitted dose and the fine particle dose (fine particle dose = micrograms acilidium bromide in the emitted dose below a cut-off aerodynamic threshold of 5 micrometer) are subjected to the same variation as specified for the metered dose and are proportional to the metered dose. For example, a metered nominal dose of about 200 micrograms corresponds to about 180 micrograms emitted dose, and about 60 micrograms Fine Particle dose.

[0015] Packaging of the formulation may be suitable for unit dose or multi-dose delivery. In the case of multi-dose delivery, the formulation can be pre-metered or metered in use. Dry powder inhalers are thus classified into three groups: (a) single dose, (b) multiple unit dose and (c) multi dose devices.

[0016] Formulations generally contain a powder mix for inhalation of the compounds of the invention and a suitable powder base (carrier substance) such as lactose or starch. Use of lactose is preferred. Each capsule or cartridge may generally contain between 2μg and 400μg of each therapeutically active ingredient. Alternatively, the active ingredient(s) may be presented without excipients.

[0017] For single dose inhalers of the first type, single doses have been weighed by the manufacturer into small containers, which are mostly hard gelatine capsules. A capsule has to be taken from a separate box or container and inserted into a receptacle area of the inhaler. Next, the capsule has to be opened or perforated with pins or cutting blades in order to allow part of the inspiratory air stream to pass through the capsule for powder entrainment or to discharge the powder from the capsule through these perforations by means of centripetal force during inhalation. After inhalation, the emptied capsule has to be removed from the inhaler again. Mostly, disassembling of the inhaler is necessary for inserting and removing the capsule, which is an operation that can be difficult and burdensome for some patients. Other drawbacks related to the use of hard gelatine capsules for inhalation powders are (a) poor protection against moisture uptake from the ambient air, (b) problems with opening or perforation after the capsules have been exposed previously to extreme relative humidity, which causes fragmentation or induration, and (c) possible inhalation of capsule fragments. Moreover, for a number of capsule inhalers, incomplete expulsion has been reported.

[0018] Some capsule inhalers have a magazine from which individual capsules can be transferred to a receiving chamber, in which perforation and emptying takes place, as described in WO 92/03175. Other capsule inhalers have revolving magazines with capsule chambers that can be brought in line with the air conduit for dose discharge (e.g. WO 91/02558 and GB 2242134). They comprise the type of multiple unit dose inhalers together with blister inhalers, which have a limited number of unit doses in supply on a disk or on a strip.

[0019] Blister inhalers provide better moisture protection of the medicament than capsule inhalers. Access to the powder is obtained by perforating the cover as well as the blister foil, or by peeling off the cover foil. When a blister strip is used instead of a disk, the number of doses can be increased, but it is inconvenient for the patient to replace an empty strip. Therefore, such devices are often disposable with the incorporated dose system, including the technique used to transport the strip and open the blister pockets.

[0020] Multi-dose inhalers do not contain pre-measured quantities of the powder formulation. They consist of a relatively large container and a dose measuring principle that has to be operated by the patient. The container bears multiple doses that are isolated individually from the bulk of powder by volumetric displacement. Various dose measuring principles exist, including rotatable membranes (e.g. EP 0096715) or disks (e.g. GB 2041763; EP 0424796; DE 4239402 and EP 0874533), rotatable cylinders (e.g. EP 0166294; GB 2165159 and WO 92/09322) and rotatable frustums (e.g. WO 92/00771), all having cavities which have to be filled with powder from the container. Other multi-dose devices have measuring slides (e.g. US 5201308 and WO 97/00703) or measuring plungers with a local or circumferential recess to displace a certain volume of powder from the container to a delivery chamber or an air conduit e.g. EP 0505321, WO 92/04068 and WO 92/04928.

[0021] Reproducible dose measuring is one of the major concerns for multi dose inhaler devices. The powder formulation has to exhibit good and stable flow properties, because filling of the dose measuring cups or cavities is mostly under the influence of the force of gravity. For reloaded single dose and multiple unit dose inhalers, the dose measuring accuracy and reproducibility can be guaranteed by the manufacturer. Multi dose inhalers on the other hand, can contain a much higher number of doses, whereas
the number of handlings to prime a dose is generally lower.

[0022] Because the inspiratory air stream in multi-dose devices is often straight across the dose measuring cavity, and because the massive and rigid dose measuring systems of multi-dose inhalers cannot be agitated by this inspiratory air stream, the powder mass is simply entrained from the cavity and little de-agglomeration is obtained during discharge.

[0023] Consequently, separate disintegration means are necessary. However in practice, they are not always part of the inhaler design. Because of the high number of doses in multi-dose devices, powder adhesion onto the inner walls of the air conduits and the de-agglomeration means must be minimized and/or regular cleaning of these parts must be possible, without affecting the residual doses in the device. Some multi-dose inhalers have disposable drug containers that can be replaced after the prescribed number of doses has been taken (e.g. WO 97/000703). For such semi-permanent multi-dose inhalers with disposable drug containers, the requirements to prevent drug accumulation are even stricter.

[0024] In a preferred embodiment, the acclidinium is administered via a breath-activated, multidose, dry powder inhaler, calibrated to permit daily dosing of 200 (plus/minus 10%) micrograms metered nominal dose of acclidinium. An especially preferred inhaler device for this purpose is Genuair®, (formerly known as Novolizer SD2FL), or as described in WO 97/000703, WO 03/000325, or WO 03/061742.

[0025] Apart from applications through dry powder inhalers the compositions of the invention can be administered in aerosols which operate via propellant gases or by means of so-called atomisers or nebulizers, via which solutions or suspensions of pharmacologically-active substances can be sprayed under high pressure so that a mist of inhalable particles results.

[0026] Medicaments for administration by inhalation desirably have a controlled particle size. The optimum particle size for inhalation into the bronchial system is usually 1-10μm, preferably 2-5μm. Particles having a size above 20μm are generally too large when inhaled to reach the small airways. To achieve these particle sizes the particles of the active ingredient as produced may be size reduced by conventional means eg by micronisation or supercritical fluid techniques. The desired fraction may be separated out by air classification or sieving. Preferably, the particles will be crystalline.

[0027] Achieving a high dose reproducibility with micronised powders is difficult because of their poor flowability and extreme agglomeration tendency. To improve the efficiency of dry powder compositions, the particles should be large while in the inhaler, but small when discharged into the respiratory tract. Thus, an excipient, for example a mono-, di- or polysaccharide or sugar alcohol, e.g., such as lactose, mannitol or glucose is generally employed. The particle size of the excipient will usually be much greater than the inhaled medicament within the present invention. When the excipient is lactose it will typically be present as lactose particles, preferably crystalline alpha lactose monohydrate, e.g. having an average particle size range of 20-1000 μm, preferably in the range of 90-150 μm. The median particle size approximately corresponds to the average and is the diameter where 50 mass-% of the particles have a larger equivalent diameter, and the other 50 mass-% have a smaller equivalent diameter. Hence the average particle size is generally referred to in the art as equivalent d50. The distribution of particle size around may affect flow properties, bulk density, etc. Hence to characterize a particle size diameter, other equivalent diameters can be used in addition to d50, such as d10 and d90. d10 is the equivalent diameter where 10 mass-% of the particles have a smaller diameter (and hence the remaining 90% is coarser). d90 is the equivalent diameter where 90 mass-% of the particles have a smaller diameter. In one embodiment, the lactose particles for use in formulations of the invention have a d10 of 90 - 160 μm, a d50 of 170 - 270 μm, and d90 of 290 - 400 μm.

[0028] Suitable lactose materials for use in the present invention are commercially available, e.g., from DMW Internacional (Respitose GR-001, Respitose SV-001, Respitose SV-003); Meggle (Capsulac 60, Inhalac 70, Capsulac 60 INH); and Borculo Domo (Lactohale 100-200, Lactohale 200-300, and Lactohale 100-300).

[0029] The ratio between the lactose particles and the acclidinium by weight will depend on the inhaler device used, but is typically, e.g., 5:1 to 200:1, for example 50:1 to 150:1, e.g., 60-70:1.

[0030] In a preferred embodiment, the acclidinium is administered in the form of a dry powder formulation of acclidinium bromide in admixture with lactose, in a ratio by weight of acclidinium to lactose of 1:100 to 1:150, suitable for administration via a dry powder inhaler, wherein the acclidinium particles have an average particle size of from 2 to 5μm in diameter, e.g., less than 3 μm in diameter, and the lactose particles have a d10 of 90 - 160 μm, a d50 of 170 - 270 μm, and d90 of 290 - 400 μm.

[0031] Additional active agents such as β2-agonists, PDE IV inhibitors, corticosteroids, leukotriene D4 antagonists, inhibitors of egfr-kinase, p38 kinase inhibitors or NK1 receptor agonists may be utilized in the methods and formulations of the inventions.
example, the invention provides acidinium formulations as described herein further comprising an effective amount of one or more such additional active agents, e.g. further comprising an effective amount of a β2-agonist and/or a PDE IV inhibitor and/or a corticosteroid. Described herein are methods for treating asthma comprising administering an acidinium formulation as described herein and further comprising administering simultaneously an effective amount of one or more such additional active agents, e.g. further comprising an effective amount of a β2-agonist and/or a PDE IV inhibitor and/or a corticosteroid.

[0032] β2-agonists suitable for use with the acidinium in the present invention include, e.g., arformoterol, bambuterol, bitolterol, broxaterol, carbuterol, clenbuterol, dopexamine, fenoterol, formoterol, hexoprenaline, ibuterol, isethionate, isoprorenaline, levalosalbutamol, mabuterol, meluadrine, metaproterenol, nolmilore, orciprenaline, pirbuterol, procaterol, reproterol, ritodrine, rimeutol, salbutamol, salmefamol, salmeterol, sibenadet, soterenol, sulfontoline, terbutaline, tiaramide, tulobuterol, GSK-597901, milveterol, GSK-678007, GSK-642444, GSK-159821, LAS100977 (5-2-[[6-(2,2-difluoro-2-phenylethoxy)hexyl]amino]-1(R)-hydroxyethyl]-8-hydroxyquinolin-2(1H)-one), HOKU-81, KUL-1248, carmoterol, indacaterol and 5-[2-(5,8-dieethylidene-2-yamino)-1-hydroxyethyl]-8-hydroxy-1H-quinolin-2-one, 4-hydroxy-7-[2-[[3-(2-phenylethoxy)propyl]sulfonyl]ethyl]aminoethyl]aminoethyl]-2(3H)-benzothiazolone, 1-(2-fluoro-4-hydroxyphenyl)-2-[4-(1-benzimidazolyl)-2-methyl-2-butyramino]ethanol, 1-[2-(4-methoxybenzylamino)-4-hydroxyphenyl]-2-[4-[(1-benzimidazolyl)-2-methyl-2-butyramino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-N,N-dimethylaminophenyl)-2-methyl-2-propylaminol]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-methoxyphenyl)-2-methyl-2-propylaminol]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-n-butyloxophenyl)-2-methyl-2-propylaminol]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-methoxyphenyl)-1,2,4-triazol-3-yl]-2-methyl-2-butyramino]ethanol, 5-hydroxy-8-[(1-hydroxy-2-isopropylaminobutyl)-2H-1,4-benzoxazin-3-(4H)-one, 1-(4-amino-3-chloro-5-trifluoromethylphenyl)-1-tert-butyramino]ethanol and 1-(4-ethoxyacarbonylamino-3-cyano-5-fluorophenyl)-2-(tert-butyramino)ethanol optionally in the form of their racemates, their enantiomers, their diastereomers, and mixtures thereof, and optionally their pharmaceutically-compatible acid addition salts.

[0033] The preferred β2-agonists to be used in the combinations of the invention are: arformoterol, bambuterol, bitolterol, broxaterol, carbuterol, clenbuterol, dopexamine, fenoterol, formoterol, hexoprenaline, ibuterol, isethionate, isoprorenaline, levalosalbutamol, mabuterol, meluadrine, nolmilore, orciprenaline, pirbuterol, procaterol, (R,R)-formoterol, reproterol, ritodrine, rimeutol, salbutamol, salmefamol, sibenadet, soterenol, sulfontoline, terbutaline, tulobuterol, GSK-597901, milveterol, LAS100977 (5-2-[[6-(2,2-difluoro-2-phenylethoxy)hexyl]amino]-1(R)-hydroxyethyl]-8-hydroxyquinolin-2(1H)-one), KUL-1248, carmoterol and indacaterol optionally in the form of their racemates, their enantiomers, their diastereomers, and mixtures thereof, and optionally their pharmaceutically-compatible acid addition salts.

[0034] Since the M3 antagonists of the invention have a long duration of action, it is preferred that they are combined with long-acting β2-agonists (also known as LABAs). The combined drugs could thus be administered once or twice a day.

[0035] Particularly preferred LABAs are formoterol, salmeterol and GSK-597901, milveterol, LAS100977 (5-2-[[6-(2,2-difluoro-2-phenylethoxy)hexyl]amino]-1(R)-hydroxyethyl]-8-hydroxyquinolin-2(1H)-one), KUL-1248, carmoterol and indacaterol optionally in the form of their racemates, their enantiomers, their diastereomers and mixtures thereof, and optionally their pharmaceutically-compatible acid addition salts. More preferred are salmeterol, formoterol, LAS100977 (5-2-[[6-(2,2-difluoro-2-phenylethoxy)hexyl]amino]-1(R)-hydroxyethyl]-8-hydroxyquinolin-2(1H)-one), and QAB-149. Still more preferred are salmeterol, formoterol and LAS100977 (5-2-[[6-(2,2-difluoro-2-phenylethoxy)hexyl]amino]-1(R)-hydroxyethyl]-8-hydroxyquinolin-2(1H)-one), in particular salmeterol xinafoate and formoterol fumarate and LAS100977 (5-2-[[6-(2,2-difluoro-2-phenylethoxy)hexyl]amino]-1(R)-hydroxyethyl]-8-hydroxyquinolin-2(1H)-one).

[0036] For example, the invention provides a pharmaceutical composition for use by inhalation comprising acidinium in the form of a dry powder of a pharmaceutically acceptable salt, e.g., bromide, in admixture with a pharmaceutically acceptable carrier, e.g., lactose particles, together with formoterol fumarate, (i) comprising a single metered nominal dose of acidinium equivalent to 200 (plus/minus 10%) micrograms acidinium bromide together with a single metered nominal dose of 5-25 micrograms (e.g. 6, 8.5, 12, 18 or 24 micrograms, for example 12 micrograms) formoterol fumarate or (ii) in a multidose dry powder inhaler device calibrated to provide a metered nominal dose of acidinium equivalent to 200 micrograms (plus/minus 10%) acidinium bromide together with a metered nominal dose of 5-25 micrograms (e.g. 6, 8.5, 12, 18 or 24 micrograms, for example 12 micrograms) formoterol fumarate.

[0037] The pharmaceutical composition for use by inhalation comprising acidinium and a β2-agonist, for example, formoterol or LAS100977 (5-2-[[6-(2,2-difluoro-2-phenylethoxy)hexyl]amino]-1(R)-hydroxyethyl]-8-hydroxyquinolin-2(1H)-one), can be administrated one or more times per day. Preferably once or twice a day.

[0038] Examples of suitable PDE4 inhibitors that can be combined with acidinium in the present invention are benafentamine dimaleate, etazolate, denbufylline, rolipram, cipamfylline, zaradverine, arofinylidene, flaminast, tipelukast, tofinitast piclamilast, flaminast, tipelukast, tofinitast piclamilast, flaminast, tipelukast, tofinitast piclamilast,
tolafentrine, mesopram, drotaverine hydrochloride, lirilmist, roflumilast, cilmilast, ogilmilast, apramilast, 6-{[3,4-Diethoxymethyl]thiazoi-2-yl}pyridine-2-carboxylic acid (tornilast), (R)-( )-4-{[2-(3-Cyclopentoxyl-4-methoxyphenyl)-2-phenylethyl]pyridine (CDP-840), N-(3,5-Dichloro-4-pyridinyl)-2-{[4-fluorobenzyl]-5-hydroxy-1H-indol-3-yl}-2-oxoacetamide (GSK-842470), 9-(2-Fluorobenzyl)-8-N6-methyl-2-(trifluoromethyl)adenine (NCS-813), N-(3,5-Dichloro-4-pyridinyl)-8-methoxyquinoline-5-carboxamide (D-4418), N-[9-Methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydropropyrolo[2,3,1-ik][1,4]benzodiazepin-3-(R)-yl]pyridine-4-carboxamide, 3-{[(Cyclopentoxyl)-4-methoxybenzyl]-6-(ethylamino)-8-isopropyl-3H-purine hydrochloride (V-11294A), 6-[3-(N,N-Dimethylcarbamoyl)phenylsulfonyl]-4-(3-methoxyphenylamino)-8-methoxyquinoline-3-carboxamide hydrochloride (GSK-250666), 4-[6,7-Diethoxy-2,3-bis(hydroxymethyl)napthalen-1-yl]-1-(2-methoxyethyl)pyridin-2(1H)-one (T-440), (-)-trans-2-[3-(N-Cyclopropylcarbamoyl)-4-oxo-1,4-dihydro-1,8-naphthyridin-1-yl]-3-fluorobiphenyl-4-ylcyclopropane carboxylic acid (MK-0873), CDC-801, UK-500001, BLX-914, 1,2-carboxhydroxy-4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-one, cis-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol, 5(S)-3-[Cyclopentoxyl]-4-methoxyphenyl]-3(S)- (3-methylbenzyl)pyperidin-2-one (PFL-455903), ONO-8126 (Eur Respir J 2003, 22(Suppl. 45): Abst 2557) and the compounds claimed in the PCT patent applications number WO03/097613, WO2004/058729, WO 2005/049581, WO 2005/126393 and WO 2005/123692.

[0039] Examples of suitable corticosteroids and glucocorticoids that can be combined with aclidinium in the present invention are prenisolone, methylprednisolone, dexamethasone, dexamethasone cipiclate, nafliocort, deflazacort, haloperdone acetate, budesonide, beclomethasone dipropionate, hydrocortisone, triamcinolone acetonide, fluocinolone acetonide, fluocinonide, clocortolone pivalate, methylprednisolone acetonate, dexamethasone palmitate, tiopredane, hydrocortisone acetate, prednicarbate, alclometasone dipropionate, Butiaccort propionate, RPR-106541, halometasone, methylprednisolone suleptanate, mometasone furoate, nimoxolone, prednisolone farnesylate, ciclesonide, desoprodone propionate, fluticasone propionate, fluticasone furoate, halobetasol propionate, letoprednol elobenate, betamethasone butyrate propionate, flunisolide, prednisone, dexamethasone sodium phosphate, triamcinolone, betamethasone 17-valerate, betamethasone, betamethasone dipropionate, 21-Chloro-11beta-hydroxy-17alpha-[2-(methylsulfanyl)acetoxy]-4-pregnen-3,20-dione, Desisobutyliciclesonide, hydrocortisone acetate, hydrocortisone sodium succinate, NS-126, prednisolone sodium phosphate, hydrocortisone propionate prednisolone sodium metasulfozoate and clobetasol propionate, especially budesonide or mometasone.

[0040] For example, the pharmaceutical composition for use by inhalation may comprise aclidinium in the form of a dry powder of a pharmaceutically acceptable salt, e.g., bromide, in admixture with a pharmaceutically acceptable carrier, e.g., lactose particles, together with mometasone furoate, (i) comprising a single metered nominal dose of aclidinium equivalent to 200 micrograms (plus/minus 10%) aclidinium bromide together with a single metered nominal dose of about 100-900 µg (e.g. 100, 110, 200, 220, 300, 330, 400, 440, 800 or 880 µg, for example 200-450 µg, e.g. 220 or 440 µg) mometasone furoate, or (ii) in a multidose dry powder inhaler device calibrated to provide a metered nominal dose of aclidinium equivalent to 200 micrograms (plus/minus 10%) aclidinium bromide together with a metered nominal dose of about 100-900 µg (e.g. 100, 110, 200, 220, 300, 330, 400, 440, 800 or 880 µg, for example 200-450 µg, e.g. 220 or 440 µg) mometasone furoate.

[0041] The pharmaceutical composition for use by inhalation comprising aclidinium and a corticosteroid, for example mometasone furoate, can be administered one or more times per a day. Preferably once or twice a day.

[0042] The pharmaceutical composition used in the invention may comprise aclidinium, a β2-agonist as defined above and a corticosteroid, as defined above. Most preferred β2-agonists are selected from LAS100977 ((5-[(2-[(6-[(2,2-difluoro-2-phenylethoxy)hexy]aminol)-1(R)-hydroxyethyl]-8-hydroxyquinolin-2(1H)-one) and formoterol. Most preferred corticosteroid is a mometasone furoate. These triple combinations are suitable for administration once or twice a day.

EXAMPLE 1

[0043] Methods: Patients with moderate to severe stable COPD were randomized to receive double-blind, once-daily treatment with aclidinium (25, 50, 100, 200, or 400 µg), placebo, or open-label tiotropium 18 µg for 4 weeks. Spirometric measurements were performed at 22-24 h after the first dose and then at weekly intervals, and from 0.5-6 h post-administration on Day 1 and at Week 4 (Day 29).

[0044] Results: The ITT population included 460 patients. Aclidinium dose-dependently increased trough FEV1 on Day 29 (table).

Mean change from baseline in trough FEV1 on Day 29
<table>
<thead>
<tr>
<th></th>
<th>Acidinium (double-blind)</th>
<th>Tiotropium (open-label)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25 µg</td>
<td>100 µg</td>
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<tr>
<td></td>
<td>50 µg</td>
<td>200 µg</td>
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<tr>
<td></td>
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<td>Mean Δ, ml</td>
<td>39</td>
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<td></td>
<td>36</td>
<td>128*</td>
</tr>
<tr>
<td></td>
<td>83</td>
<td>161*</td>
</tr>
</tbody>
</table>

*p<0.05 vs placebo

[0046] Unlike tiotropium, the bronchodilatory effect of acidinium during the first 6 h post-dose on Day 29 was comparable to that on Day 1 (all doses). Time to peak FEV₁ was achieved at 3 h post-dose for acidinium 100-400 µg. Acidinium was well tolerated, with no dose-dependent effect on ECG, laboratory parameters or adverse events.

[0047] Conclusion: Acidinium produced sustained bronchodilation over 24 h and was well tolerated. Acidinium 200 and 400 µg had comparable bronchodilatory effects to open-label tiotropium 18 µg. Based on the efficacy and tolerability data, acidinium 200 µg was selected as the investigational dose for a future long-term clinical trial in COPD.

REFERENCES CITED IN THE DESCRIPTION

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Patentkrav

1. Farmaceutisk sammensætning omfattende aclidinium i form af et tørpulver af et farmaceutisk acceptabelt salt blandet med en farmaceutisk acceptabel tørpulverbærer, der tilvejebringer en afmålt nominel dosis aclidinium ækvivalent med 200 mikrogram (plus/minus 10 %) aclidiniumbromid til anvendelse ved inhalation i behandlingen af astma.

2. Farmaceutisk sammensætning til anvendelse ifølge krav 1 i form af en enkeltdosistørpulverformulering omfattende en enkelt afmålt nominel dosis aclidinium ækvivalent med 200 mikrogram (plus/minus 10 %) aclidiniumbromid.

3. Farmaceutisk sammensætning til anvendelse ifølge krav 1 i form af en multidosistørpulverformulering til administration i en multitørpulverinhalatoranordning, der er kalibret til at tilvejebringe en afmålt nominel dosis aclidinium ækvivalent med 200 mikrogram (plus/minus 10 %) aclidiniumbromid.

4. Farmaceutisk sammensætning til anvendelse ifølge et hvilket som helst af de foregående krav, hvor (a) det farmaceutisk acceptable salt af aclidinium er aclidiniumbromid, og/eller (b) den farmaceutisk acceptable bærer er lactosepartikler.

5. Farmaceutisk sammensætning til anvendelse ifølge et hvilket som helst af de foregående krav, hvor vægtforholdet mellem aclidinium og bærestof er fra 1:50 til 1:150.

6. Farmaceutisk sammensætning til anvendelse ifølge krav 5, hvor vægtforholdet mellem aclidinium og bærestof er fra 1:100 til 1:150.

7. Farmaceutisk sammensætning til anvendelse ifølge et hvilket som helst af de foregående krav, hvor (a) den gennemsnitlige partikeldiameter af aclidinium
er inden for 2-5 μm, og/eller (b) bærerpartiklerne har en d10 på 90 - 160 μm, d50 på 170 - 270 μm og d90 på 290 – 400 μm.


9. Farmaceutisk sammensætning til anvendelse ifølge krav 8, hvor det supplerende aktive middel er valgt fra formoterol, salmeterol, budesonid og fluticasonpropionat, i fri eller farmaceutisk acceptabel saltform.

10. Farmaceutisk sammensætning til anvendelse ifølge krav 9, hvor (a) det supplerende aktive middel er formoterolfumarat i en mængde på 5-25 mikrogram pr. dosis, eller (b) det supplerende aktivt middel er formoterolfumarat i en mængde på 6 mikrogram pr. dosis, eller (c) det supplerende aktive middel er formoterolfumarat i en mængde på 12 mikrogram pr. dosis.

11. Acidinium i fri eller farmaceutisk acceptabel saltform til anvendelse ved behandling af astma hos en patient med behov for en sådan behandling, hvilken anvendelse omfatter administration ved inhalation én eller to gange dagligt af en afmålt nominel dosis acidinium ækvivalent med 200 mikrogram (plus/minus 10 %) acidiniumbromid.

12. Acidinium i fri eller farmaceutisk acceptabel saltform for anvendelse ifølge krav 11, hvilken anvendelse omfatter administration af en farmaceutisk sammensætning ifølge et hvilket som helst af kravene 1-10.

14. Acidinium i fri eller farmaceutisk acceptabel saltform for anvendelse ifølge krav 13, hvor det supplerende aktive middel er valgt fra formoterol, salmeterol, budesonid og fluticasonpropionat, i fri eller farmaceutisk acceptabel saltform.

15. Acidinium i fri eller farmaceutisk acceptabel saltform for anvendelse ifølge krav 14, hvor (a) det supplerende aktive middel er formoterolfumarat i en mængde på 5-25 mikrogram pr. dosis, eller (b) det supplerende aktive middel i formoterolfumarat i en mængde på 6 mikrogram pr. dosis, eller (c) det supplerende aktive middel er formoterolfumarat i en mængde på 12 mikrogram pr. dosis.

16. Anvendelse af acidinium i fri eller farmaceutisk acceptabel saltform i fremstillingen af et medikament til behandling af astma hos en patient med behov for en sådan behandling, hvilken anvendelse omfatter administration ved inhalation én eller to gange dagligt af en afmålt nominel dosis acidinium ækvivalent med 200 mikrogram (plus/minus 10 %) acidiniumbromid.

17. Anvendelse ifølge krav 16, hvor anvendelsen omfatter administration af en farmaceutisk sammensætning som defineret i et hvilket som helst af kravene 1 til 10.

18. Multitørpulverinhaltoranordning omfattende acidinium, der er kalibreret til at indgive, efter aktivering, en afmålt nominel dosis acidinium ækvivalent med 200 mikrogram (plus/minus 10 %) acidiniumbromid.