

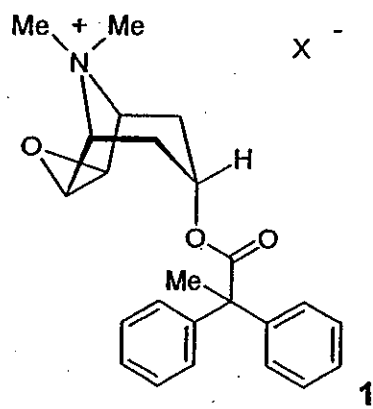
Medicaments containing betamimetic drugs and a novel anticholinesterase drug

The present invention relates to pharmaceutical compositions based on beta₂ agonists with a long-lasting effect and salts of a new anticholinergic, processes for preparing them and their use in the treatment of respiratory complaints.

Description of the invention

The present invention relates to pharmaceutical compositions based on beta₂ agonists with a long-lasting effect and salts of a new anticholinergic 1, processes for preparing them and their use in the treatment of respiratory complaints.

In a first aspect of the present invention, there is provided pharmaceutical compositions, characterised in that they contain one or more salts of formula 1



wherein

X⁻ denotes an anion with a single negative charge, preferably an anion selected from the group consisting of chloride, bromide, iodide, sulphate, phosphate, methanesulphonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate and p-toluenesulphonate,

combined with one or more betamimetics (2), optionally in the form of the enantiomers, mixtures of the enantiomers or in the form of the racemates thereof, optionally in the form of the solvates or hydrates and optionally together with a pharmaceutically acceptable excipient.

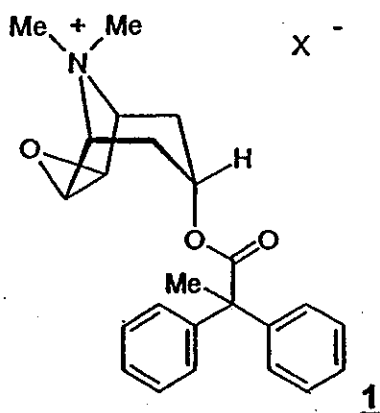
In a second aspect of the present invention, there is provided inhalable powder according to the pharmaceutical composition as defined above, characterised in that the excipient has a maximum average particle size of up to 250 μm , preferably between 10 and 150 μm .

In a third aspect of the present invention, there is provided propellant-containing inhalable aerosol according to the pharmaceutical composition as defined above, characterised in that it contains, as propellant gas, hydrocarbons such as n-propane, n-butane or isobutane or halohydrocarbons such as chlorinated and/or fluorinated derivatives of methane, ethane, propane, butane, cyclopropane or cyclobutane.

In a fourth aspect of the present invention, there is provided inhalable solution according to the pharmaceutical composition as defined above, characterized in that it optionally contains other co-solvents and/or excipients.

In a fifth aspect of the present invention, there is provided a use of a composition as defined above for preparing a medicament for the treatment of inflammatory or obstructive respiratory complaints, particularly asthma or COPD.

The anticholinergic agents disclosed are the salts of formula 1



wherein

X^- denotes an anion with a single negative charge, preferably an anion selected from the group consisting of chloride, bromide, iodide, sulphate, phosphate, methanesulphonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate and p-toluenesulphonate.

Preferably, the salts of formula 1 are used wherein

X⁻ denotes an anion with a single negative charge selected from among the chloride, bromide, 4-toluenesulphonate and methanesulphonate, preferably bromide.

Most preferably, the salts of formula 1 are used wherein

X⁻ denotes an anion with a single negative charge selected from among the chloride, bromide and methanesulphonate, preferably bromide.

Particularly preferred is the salt of formula 1 wherein X⁻ denotes bromide.

Anticholinergics may appropriately be used to treat a number of diseases.

Particular mention should be made, for example, of the treatment of asthma or COPD (chronic obstructive pulmonary disease). For treating these diseases WO 92/16528 proposes, for example, anticholinergics which have a scoline, tropenol or tropine basic structure.

The problem on which WO 92/16528 is based is the preparation of anticholinergically active compounds which are characterised by their long-lasting activity. To solve this problem WO 92/16528 discloses *inter alia* benzilic acid esters of scoline, tropenol or tropine.

For treating chronic diseases it is often desirable to prepare pharmaceutical compositions with a longer-lasting effect. This will generally ensure that the concentration of the active substance needed to achieve the therapeutic effect is present in the body for a longer period of time without the need for the pharmaceutical composition to be administered repeatedly and all too frequently. Moreover, if an active substance is administered at longer intervals of time, this contributes to the feeling of well-being of the patient to a considerable degree. It is particularly desirable to provide a pharmaceutical composition which can be used to therapeutically good effect by administering it once a day (single dose). A single application per day has the advantage that the patient can become accustomed relatively quickly to the regular taking of the medicament at a particular time of the day.

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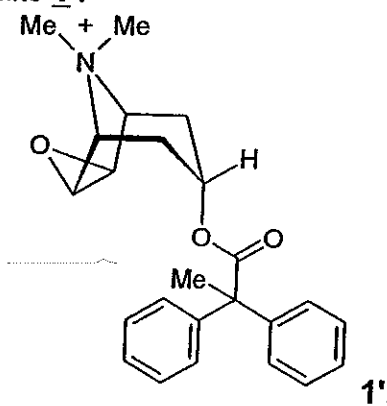
If it is to be used as a medicament for administration once a day, the active substance which is to be given must meet particular requirements. First of all, the desired onset of the activity after the administration of the pharmaceutical composition should occur relatively quickly and ideally the activity should remain as constant as possible over a fairly lengthy ensuing period. On the other hand the duration of activity of the pharmaceutical composition should not greatly exceed a period of about one day. Ideally, an active substance should have an activity profile such that the preparation of a pharmaceutical composition which is intended to be administered once a day and contains the active substance in therapeutically appropriate doses can be properly controlled.

It has been found that the esters of scoline, tropenol or tropine disclosed in WO 92/16528 do not meet these more stringent requirements. Because of their extremely long duration of activity, significantly exceeding the period of about one day specified above, they cannot be used therapeutically in a single once-a-day dose. The salts of formula 1 however meet this requirement.

Surprisingly, an unexpectedly beneficial therapeutic effect, particularly a synergistic effect can be observed in the treatment of inflammatory and/or obstructive diseases of the respiratory tract if the anticholinergic of formula 1 is used with one or more betamimetics 2. In view of this synergistic effect the pharmaceutical combinations disclosed herein can be used in smaller doses than would be the case with the individual compounds used in monotherapy in the usual way. Unwanted side effects such as may occur when beta2 agonists are administered, for example, are thus reduced. Undesirable side effects in this context are, in particular, the stimulant effects on the heart which are sometimes caused by betamimetics, especially tachycardia, palpitations, angina-pectoris-like pain and arrhythmia.

The effects mentioned above may be observed both when the two active substances are administered simultaneously in a single active substance formulation and when they are administered successively in separate formulations. It is preferable to administer the two active substance ingredients simultaneously in a single formation as disclosed herein.

Any reference to the compound 1' is to be regarded as a reference to the pharmacologically active cation of the following formula contained in the salts 1:



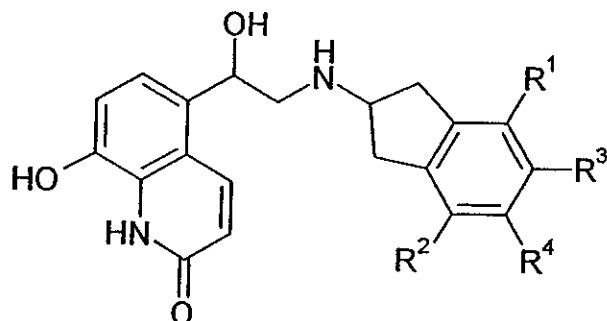
In the pharmaceutical combinations mentioned above the active substances may be combined in a single preparation or contained in two separate formulations. Pharmaceutical compositions which contain the active substances 1 and 2 in a single preparation are preferred.

Salmeterol salts or formoterol salts are preferably used as the long-acting betamimetics 2. Any reference to the term betamimetics

2 also includes a reference to the relevant enantiomers or mixtures thereof.

Accordingly, any reference to the preferred compounds 2, the salts of salmeterol and formoterol, also includes the relevant enantiomeric salts of *R*-salmeterol, *S*-salmeterol, *R,R*-formoterol, *S,S*-formoterol, *R,S*-formoterol, *S,R*-formoterol and the mixtures thereof, while the enantiomeric salts of *R*-salmeterol and *R,R*-formoterol are of particular importance. The compounds 2 may also be present in the form of the hydrates or solvates thereof.

The long-acting betamimetics 2 may also be the salts of the compounds of formula 2a',

2a'

wherein

- R¹ and R² - which may be identical or different denote hydrogen or C₁-C₄-alkyl;
 R³ and R⁴ - which may be identical or different denote hydrogen, C₁-C₄-alkyl, -O-
 5 C₁-C₄-alkyl,
 - C₁-C₄-alkylene-O-C₁-C₄-alkyl or
 R³ and R⁴ together denote one of the bridging groups
 - C₁-C₄-alkylene- or -O-C₁-C₄-alkylene-O-.

- 10 Preferably, salts of the compounds of formula 2a' wherein

- R¹ and R² - which may be identical or different denote hydrogen, methyl or ethyl;
 R³ and R⁴ - which may be identical or different denote hydrogen, methyl, ethyl,
 15 propyl, butyl, methoxy, ethoxy, methoxymethyl, or methoxyethyl, or
 R³ and R⁴ together denote one of the bridging groups
 propylene, butylene, -O-ethylene-O- or -O-propylene-O-

are used in the combinations as disclosed herein.

- 20 More preferably, salts of the compounds of formula 2a' wherein

- R¹ and R² - which may be identical or different denote hydrogen or ethyl,
 preferably hydrogen;
 R³ and R⁴ - which may be identical or different denote hydrogen, methyl, ethyl,
 25 propyl, butyl or methoxymethyl or
 R³ and R⁴ together denote one of the bridging groups
 butylene or -O-ethylene-O-

are used in the combinations as disclosed herein.

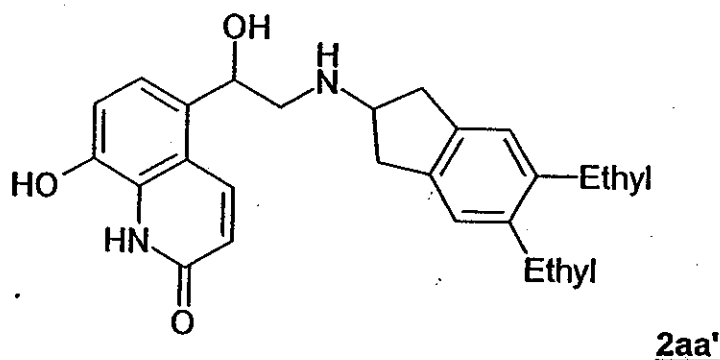
Most preferably, the salts of the following compounds of formula 2a' wherein

- a) R^1 and R^2 denote hydrogen and R^3 and R^4 denote ethyl; or
- b) R^1 and R^2 denote hydrogen and R^3 and R^4 denote methyl; or
- c) R^1 and R^2 denote ethyl and R^3 and R^4 denote hydrogen; or
- d) R^1 and R^2 denote hydrogen and R^3 and R^4 together denote butylene; or
- e) R^1 and R^2 denote hydrogen and R^3 and R^4 together denote -O-ethylene-O-; or
- f) R^1 and R^2 denote hydrogen and R^3 and R^4 denote tert.-butyl or
- g) R^1 and R^2 denote hydrogen and R^3 and R^4 denote iso-propyl; or
- h) R^1 and R^2 denote hydrogen and R^3 and R^4 denote methoxymethyl

are used in the combinations as disclosed herein.

The compounds of formula 2a' are known from WO00/75114.

Of the compounds mentioned above, the structure defined in a), wherein R^1 and R^2 denote hydrogen and R^3 and R^4 denote ethyl, are exceptionally important in the pharmaceutical combinations. The acid addition salt of this compound is hereinafter referred to as compound 2aa, while any reference to the free base of this compound is characterised by the designation 2aa' according to the following formula :



In the pharmaceutical compositions disclosed, the salts of the compounds of formula 2a' may be present in the form of their racemates,

enantiomers or mixtures thereof. The separation of the enantiomers from the racemates may be carried out using methods known in the art (e.g. by chromatography on chiral phases, etc.) If the salts of the compounds of formula 2a' are used in the form of their enantiomers, it is particularly preferable to use the enantiomers in the R configuration at the C-OH group.

The alkyl groups used, unless otherwise stated, are branched and unbranched alkyl groups having 1 to 4 carbon atoms. Examples include: methyl, ethyl, propyl or butyl. The groups methyl, ethyl, propyl or butyl may optionally also be referred to by the abbreviations Me, Et, Prop or Bu. Unless otherwise stated, the definitions propyl and butyl also include all possible isomeric forms of the groups in question. Thus, for example, propyl includes n-propyl and iso-propyl, butyl includes iso-butyl, sec. butyl and tert.-butyl, etc.

The alkylene groups used, unless otherwise stated, are branched and unbranched double-bonded alkyl bridges with 1 to 4 carbon atoms. Examples include: methylene, ethylene, propylene or butylene.

The alkyloxy groups used (also known as -O-C₁-C₄-alkyl groups), unless otherwise stated, are branched and unbranched alkyl groups with 1 to 4 carbon atoms which are linked via an oxygen atom. The following may be mentioned, for example: methyloxy, ethyloxy, propyloxy or butyloxy. The groups methyloxy, ethyloxy, propyloxy or butyloxy may optionally also be referred to by the abbreviations MeO, EtO, PropO or BuO. Unless otherwise stated, the definitions propyloxy and butyloxy also include all possible isomeric forms of the groups in question. Thus, for example, propyloxy includes n-propyloxy and iso-propyloxy, butyloxy includes iso-butyloxy, sec. butyloxy and tert.-butyloxy, etc. The word alkoxy may also possibly be used within the scope of the present invention instead of the word alkyloxy. The groups methyloxy, ethyloxy, propyloxy or butyloxy may optionally also be referred to as methoxy, ethoxy, propoxy or butoxy.

The alkylene-alkyloxy groups used, unless otherwise stated, are branched and unbranched double-bonded alkyl bridges with 1 to 4 carbon atoms which may be mono-, di- or trisubstituted, preferably monosubstituted, by an alkyloxy group.

Any reference to compounds 2 should be taken to mean a reference to physiologically acceptable acid addition salts thereof. Examples of physiologically acceptable acid addition salts of the betamimetics 2 are the pharmaceutically acceptable salts which are selected from among the salts of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, acetic acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid, 1-hydroxy-2-naphthalenecarboxylic acid, 4-phenylcinnamic acid, 5-(2,4-difluorophenyl)salicylic acid or maleic acid. If desired, mixtures of the abovementioned acids may also be used to prepare the salts 2.

The salts of the betamimetics 2 selected from among the hydrochloride, hydrobromide, sulphate, phosphate, fumarate, methanesulphonate, 4-phenylcinnamate, 5-(2,4-difluorophenyl)salicylate, maleate and xinafoate are preferred. Particularly preferred are the salts of 2 in the case of salmeterol selected from among the hydrochloride, sulphate, 4-phenylcinnamate, 5-(2,4-difluorophenyl)salicylate and xinafoate, of which the 4-phenylcinnamate, 5-(2,4-difluorophenyl)salicylate and especially xinafoate are particularly important. Particularly preferred are the salts of 2 in the case of formoterol selected from the hydrochloride, sulphate and fumarate, of which the hydrochloride and fumarate are particularly preferred. Of exceptional importance is formoterol fumarate. Most preferably, the salts of 2 in the case of the compound 2aa' are selected from among the hydrochloride and maleate, of which the maleate is particularly preferred.

Betamimetics which are not in the form of salts is indicated by a reference to compounds 2'. For example, the preferred betamimetics 2' which are not in salt form include the free base of formoterol, salmeterol or the compounds of formula 2a', whereas the particularly preferred compounds 2 are salmeterol xinafoate, formoterol fumarate or an acid addition salt 2a of a compound of formula 2a'.

The betamimetics 2 may possibly also be referred to as sympathomimetics or beta-2-agonists (β_2 -agonists). All these terms are to be regarded as interchangeable.

The abovementioned pharmaceutical compositions can contain, in addition to therapeutically effective quantities of 1 and 2, a pharmaceutically acceptable carrier. Disclosed are also pharmaceutical compositions which do not contain any pharmaceutically acceptable carrier in addition to therapeutically effective quantities of 1 and 2.

The use of therapeutically effective quantities of the salts 1 for preparing a pharmaceutical composition containing long-acting betamimetics 2 for treating inflammatory or obstructive diseases of the respiratory tract are further disclosed. Preferably, disclosed is the abovementioned use for preparing a pharmaceutical composition for treating asthma or COPD.

The compounds 1 and 2 may be administered simultaneously or successively, while it is preferable to administer compounds 1 and 2 simultaneously.

Disclosed herein is the use of therapeutically effect amounts of salts 1 and long-acting betamimetics 2 for treating inflammatory or obstructive respiratory complaints, particularly asthma or COPD.

The proportions in which the active substances 1 and 2 may be used in the active substance combinations disclosed are variable. Active substances 1 and 2 may possibly be present in the form of their solvates or hydrates. Depending on the choice of the compounds 1 and 2, the weight ratios vary on the basis of the different molecular weights of the various salt forms. Therefore, the weight ratios specified below were based on the cation 1' and the free bases 2' of the betamimetics salmeterol, formoterol and the compound 2aa' (= compound of formula 2a wherein R^1 and R^2 denote hydrogen and R^3 and R^4 denote ethyl) which are preferred.

The pharmaceutical combinations as disclosed may contain 1' and 2' in the case of formoterol, for example, in ratios by weight ranging from 1:10 to 300:1, preferably from 1:5 to 200:1, preferably 1:3 to 150:1, more preferably from 1:2 to 100:1.

For example, without restricting the scope of the invention thereto, preferred combinations of 1 and 2 may contain the cation 1' and formoterol 2' in the following weight ratios: 1:5, 1:4, 1:3, 1:2, 1:1, 2:1, 3:1, 4:1, 5:1, 6:1, 7:1, 8:1, 9:1, 10:1, 11:1, 12:1, 13:1, 14:1, 15:1, 16:1, 17:1, 18:1, 19:1, 20:1, 21:1, 22:1, 23:1, 24:1, 25:1, 26:1, 27:1, 28:1, 29:1, 30:1, 31:1, 32:1, 33:1, 34:1, 35:1, 36:1, 37:1, 38:1, 39:1, 40:1, 41:1, 42:1, 43:1, 44:1, 45:1, 46:1, 47:1, 48:1, 49:1, 50:1, 51:1, 52:1, 53:1, 54:1, 55:1, 56:1, 57:1, 58:1, 59:1, 60:1, 61:1, 62:1, 63:1, 64:1, 65:1, 66:1, 67:1, 68:1, 69:1, 70:1, 71:1, 72:1, 73:1, 74:1, 75:1, 76:1, 77:1, 78:1, 79:1, 80:1, 81:1, 82:1, 83:1, 84:1, 85:1, 86:1, 87:1, 88:1, 89:1, 90:1, 91:1, 92:1, 93:1, 94:1, 95:1, 96:1, 97:1, 98:1, 99:1, 100:1.

The pharmaceutical compositions containing the combinations of 1 and 2 are normally administered so that the pharmacologically active cation 1' and formoterol 2' are present together in doses of 5 to 5000 μ g, preferably from 10 to 2000 μ g, more preferably from 15 to 1000 μ g, better still from 20 to 800 μ g, preferably, from 30 to 300 μ g, preferably from 40 to 500 μ g.

For example, combinations of 1 and 2 contain a quantity of cation 1' and formoterol 2' such that the total dosage per single dose is about 10 μ g, 15 μ g, 20 μ g, 25 μ g, 30 μ g, 35 μ g, 40 μ g, 45 μ g, 50 μ g, 55 μ g, 60 μ g, 65 μ g, 70 μ g, 75 μ g, 80 μ g, 85 μ g, 90 μ g, 95 μ g, 100 μ g, 105 μ g, 110 μ g, 115 μ g, 120 μ g, 125 μ g, 130 μ g, 135 μ g, 140 μ g, 145 μ g, 150 μ g, 155 μ g, 160 μ g, 165 μ g, 170 μ g, 175 μ g, 180 μ g, 185 μ g, 190 μ g, 195 μ g, 200 μ g, 205 μ g, 210 μ g, 215 μ g, 220 μ g, 225 μ g, 230 μ g, 235 μ g, 240 μ g, 245 μ g, 250 μ g, 255 μ g, 260 μ g, 265 μ g, 270 μ g, 275 μ g, 280 μ g, 285 μ g, 290 μ g, 295 μ g, 300 μ g, 305 μ g, 310 μ g, 315 μ g, 320 μ g, 325 μ g, 330 μ g, 335 μ g, 340 μ g, 345 μ g, 350 μ g, 355 μ g, 360 μ g, 365 μ g, 370 μ g, 375 μ g, 380 μ g, 385 μ g, 390 μ g, 395 μ g, 400 μ g, 405 μ g, 410 μ g, 415 μ g, 420 μ g, 425 μ g, 430 μ g, 435 μ g, 440 μ g, 445 μ g, 450 μ g, 455 μ g, 460 μ g, 465 μ g, 470 μ g, 475 μ g, 480 μ g, 485 μ g, 490 μ g, 495 μ g, 500 μ g, 505 μ g, 510 μ g, 515 μ g, 520 μ g, 525 μ g,

530µg, 535µg, 540µg, 545µg, 550µg, 555µg, 560µg, 565µg, 570µg, 575µg, 580µg, 585µg, 590µg, 595µg, 600µg or similar. It is clear to anyone skilled in the art that the suggested dosages per single dose specified above are not to be regarded as being limited to the numerical values actually stated. Fluctuations of about $\pm 2.5 \mu\text{g}$, particularly in the decimal range, are also included, as will be apparent to the skilled man. In these dosage ranges, the active substances 1' and 2' may be present in the weight ratios given above.

For example, without restricting the scope of the invention thereto, the combinations of 1 and 2 may contain a quantity of cation 1' and formoterol 2' such that, for each single dose, 8.3µg of 1' and 2.5µg of 2', 8.3µg of 1' and 4.9µg of 2', 8.3µg of 1' and 9.8µg of 2', 8.3µg of 1' and 14.7µg of 2', 8.3µg of 1' and 19.6µg of 2', 8.3µg of 1' and 24.4µg of 2', 16.5µg of 1' and 2.5µg of 2', 16.5µg of 1' and 4.9µg of 2', 16.5µg of 1' and 9.8µg of 2', 16.5µg of 1' and 14.7µg of 2', 16.5µg of 1' and 19.6µg of 2', 16.5µg of 1' and 24.4µg of 2', 33.0µg of 1' and 2.5µg of 2', 33.0µg of 1' and 4.9µg of 2', 33.0µg of 1' and 9.8µg of 2', 33.0µg of 1' and 14.7µg of 2', 33.0µg of 1' and 19.6µg of 2', 33.0µg of 1' and 24.4µg of 2', 49.5µg of 1' and 2.5µg of 2', 49.5µg of 1' and 4.9µg of 2', 49.5µg of 1' and 9.8µg of 2', 49.5µg of 1' and 14.7µg of 2', 49.5µg of 1' and 19.6µg of 2', 49.5µg of 1' and 24.4µg of 2', 82.6µg of 1' and 2.5µg of 2', 82.6µg of 1' and 4.9µg of 2', 82.6µg of 1' and 9.8µg of 2', 82.6µg of 1' and 14.7µg of 2', 82.6µg of 1' and 19.6µg of 2', 82.6µg of 1' and 24.4µg of 2', 165.1µg of 1' and 2.5µg of 2', 165.1µg of 1' and 4.9µg of 2', 165.1µg of 1' and 9.8µg of 2', 165.1µg of 1' and 14.7µg of 2', 165.1µg of 1' and 19.6µg of 2', 165.1µg of 1' and 24.4µg of 2', 206.4µg of 1' and 2.5µg of 2', 206.4µg of 1' and 4.9µg of 2', 206.4µg of 1' and 9.8µg of 2', 206.4µg of 1' and 14.7µg of 2', 206.4µg of 1' and 19.6µg of 2', 206.4µg of 1' and 24.4µg of 2', 412.8µg of 1' and 2.5µg of 2', 412.8µg of 1' and 4.9µg of 2', 412.8µg of 1' and 9.8µg of 2', 412.8µg of 1' and 14.7µg of 2', 412.8µg of 1' and 19.6µg of 2', 412.8µg of 1' and 24.4µg of 2' are present.

If the active substance combination in which the bromide is used as the salt 1 and in which 2 denotes formoterol fumarate is used as the preferred combination of 1 and 2, the quantities of active substance 1' and 2' administered per single dose mentioned by way of example correspond to the following quantities of 1 and 2 administered per single dose: 10µg of 1 and 2.9µg

of 2, 10µg of 1 and 5.7µg of 2, 10µg of 1 and 11.5µg of 2, 10µg of 1 and 17.2µg of 2, 10µg of 1 and 22.9µg of 2, 10µg of 1 and 28.5µg of 2, 20µg of 1 and 2.9µg of 2, 20µg of 1 and 5.7µg of 2, 20µg of 1 and 11.5µg of 2, 20µg of 1 and 17.2µg of 2, 20µg of 1 and 22.9µg of 2, 20µg of 1 and 28.5µg of 2, 40µg of 1 and 2.9µg of 2, 40µg of 1 and 5.7µg of 2, 40µg of 1 and 11.5µg of 2, 40µg of 1 and 17.2µg of 2, 40µg of 1 and 22.9µg of 2, 40µg of 1 and 28.5µg of 2, 60µg of 1 and 2.9µg of 2, 60µg of 1 and 5.7µg of 2, 60µg of 1 and 11.5µg of 2, 60µg of 1 and 17.2µg of 2, 60µg of 1 and 22.9µg of 2, 60µg of 1 and 28.5µg of 2, 100µg of 1 and 2.9µg of 2, 100µg of 1 and 5.7µg of 2, 100µg of 1 and 11.5µg of 2, 100µg of 1 and 17.2µg of 2, 100µg of 1 and 22.9µg of 2, 100µg of 1 and 28.5µg of 2, 200µg of 1 and 2.9µg of 2, 200µg of 1 and 5.7µg of 2, 200µg of 1 and 11.5µg of 2, 200µg of 1 and 17.2µg of 2, 200µg of 1 and 22.9µg of 2, 200µg of 1 and 28.5µg of 2, 250µg of 1 and 2.9µg of 2, 250µg of 1 and 5.7µg of 2, 250µg of 1 and 11.5µg of 2, 250µg of 1 and 17.2µg of 2, 250µg of 1 and 22.9µg of 2, 250µg of 1 and 28.5µg of 2, 500µg of 1 and 2.9µg of 2, 500µg of 1 and 5.7µg of 2, 500µg of 1 and 11.5µg of 2, 500µg of 1 and 17.2µg of 2, 500µg of 1 and 22.9µg of 2, 500µg of 1 and 28.5µg of 2.

If the active substance combination in which 2 denotes formoterol fumarate dihydrate and the salt 1 is bromide is used as a preferred combination of 1 and 2, the quantities of active substance 1' and 2' administered per single dose mentioned by way of example correspond to the following quantities of 1 and 2 administered per single dose: 10µg of 1 and 3µg of 2, 10µg of 1 and 6µg of 2, 10µg of 1 and 12µg of 2, 10µg of 1 and 18µg of 2, 10µg of 1 and 24µg of 2, 10µg of 1 and 30µg of 2, 20µg of 1 and 3µg of 2, 20µg of 1 and 6µg of 2, 20µg of 1 and 12µg of 2, 20µg of 1 and 18µg of 2, 20µg of 1 and 24µg of 2, 20µg of 1 and 30µg of 2, 40µg of 1 and 3µg of 2, 40µg of 1 and 6µg of 2, 40µg of 1 and 12µg of 2, 40µg of 1 and 18µg of 2, 40µg of 1 and 24µg of 2, 40µg of 1 and 30µg of 2, 60µg of 1 and 3µg of 2, 60µg of 1 and 6µg of 2, 60µg of 1 and 12µg of 2, 60µg of 1 and 18µg of 2, 60µg of 1 and 24µg of 2, 60µg of 1 and 30µg of 2, 100µg of 1 and 3µg of 2, 100µg of 1 and 6µg of 2, 100µg of 1 and 12µg of 2, 100µg of 1 and 18µg of 2, 100µg of 1 and 24µg of 2, 100µg of 1 and 30µg of 2, 200µg of 1 and 3µg of 2, 200µg of 1 and 6µg of 2, 200µg of 1 and 12µg of 2, 200µg of 1 and 18µg of 2, 200µg of 1 and 24µg of 2, 200µg of 1 and 30µg of 2, 250µg of 1 and 3µg of 2, 250µg of 1 and 6µg of 2, 250µg of 1 and 12µg of 2, 250µg of 1 and 18µg of 2, 250µg of 1 and 24µg of 2, 250µg of 1 and 30µg of 2.

500µg of 1 and 3µg of 2, 500µg of 1 and 6µg of 2, 500µg of 1 and 12µg of 2, 500µg of 1 and 18µg of 2, 500µg of 1 and 24µg of 2, 500µg of 1 and 30µg of 2.

The active substance combinations may contain 1' and 2', in the case of salmeterol, for example, in ratios by weight in the range from about 1:30 to 400:1, preferably 1:25 to 200:1, preferably 1:20 to 100:1, more preferably from 1:15 to 50:1.

For example, without restricting the scope of the invention thereto, preferred combinations of 1 and 2 may contain the cation 1' and salmeterol 2' in the following ratios by weight: 1:15, 1:14, 1:13, 1:12, 1:11, 1:10, 1:9, 1:8, 1:7, 1:6, 1:5, 1:4, 1:3, 1:2, 1:1, 2:1, 3:1, 4:1, 5:1, 6:1, 7:1, 8:1, 9:1, 10:1, 11:1, 12:1, 13:1, 14:1, 15:1, 16:1, 17:1, 18:1, 19:1, 20:1, 21:1, 22:1, 23:1, 24:1, 25:1, 26:1, 27:1, 28:1, 29:1, 30:1, 31:1, 32:1, 33:1, 34:1, 35:1.

The pharmaceutical compositions as disclosed containing the combinations of 1 and 2 are usually administered so that the cation 1' and salmeterol 2' are present together in dosages of 5 to 5000µg, preferably from 10 to 2000µg, more preferably from 15 to 1000µg, even more preferably from 20 to 800µg, and preferably from 30 to 750 µg, preferably from 40 to 700µg per single dose.

For example, combinations of 1 and 2 contain an amount of 1' and salmeterol 2' such that the total dosage per single dose is about 15µg, 20µg, 25µg, 30µg, 35µg, 40µg, 45µg, 50µg, 55µg, 60µg, 65µg, 70µg, 75µg, 80µg, 85µg, 90µg, 95µg, 100µg, 105µg, 110µg, 115µg, 120µg, 125µg, 130µg, 135µg, 140µg, 145µg, 150µg, 155µg, 160µg, 165µg, 170µg, 175µg, 180µg, 185µg, 190µg, 195µg, 200µg, 205µg, 210µg, 215µg, 220µg, 225µg, 230µg, 235µg, 240µg, 245µg, 250µg, 255µg, 260µg, 265µg, 270µg, 275µg, 280µg, 285µg, 290µg, 295µg, 300µg, 305µg, 310µg, 315µg, 320µg, 325µg, 330µg, 335µg, 340µg, 345µg, 350µg, 355µg, 360µg, 365µg, 370µg, 375µg, 380µg, 385µg, 390µg, 395µg, 400µg, 405µg, 410µg, 415µg, 420µg, 425µg, 430µg, 435µg, 440µg, 445µg, 450µg, 455µg, 460µg, 465µg, 470µg, 475µg, 480µg, 485µg, 490µg, 495µg, 500µg, 505µg, 510µg, 515µg, 520µg, 525µg, 530µg, 535µg, 540µg, 545µg, 550µg, 555µg, 560µg, 565µg, 570µg, 575µg, 580µg,

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585µg, 590µg, 595µg, 600µg, 605µg, 610µg, 615µg, 620µg, 625µg, 630µg, 635µg, 640µg, 645µg, 650µg, 655µg, 660µg, 665µg, 670µg, 675µg, 680µg, 685µg, 690µg, 695µg, 700µg or similar. It is clear to anyone skilled in the art that the suggested dosages per single dose specified above are not to be regarded as being limited to the numerical values actually stated. Fluctuations of about ± 2.5 µg, particularly in the decimal range, are also included, as will be apparent to the skilled man. In these dosage ranges, the active substances 1' and 2' may be present in the weight ratios given above.

10 For example, without restricting the scope of the invention thereto, the combinations of 1 and 2 may contain a quantity of cation 1' and salmeterol 2' such that, for each single dose, 8.3µg of 1' and 12.5µg of 2', 8.3µg of 1' and 25µg of 2', 8.3µg of 1' and 50µg of 2', 8.3µg of 1' and 75µg of 2', 8.3µg of 1' and 100µg of 2', 8.3µg of 1' and 200µg of 2', 16.5µg of 1' and 12.5µg of 2', 16.5µg of 1' and 25µg of 2', 16.5µg of 1' and 50µg of 2', 16.5µg of 1' and 75µg of 2', 16.5µg of 1' and 100µg of 2', 16.5µg of 1' and 200µg of 2', 33.0µg of 1' and 12.5µg of 2', 33.0µg of 1' and 25µg of 2', 33.0µg of 1' and 50µg of 2', 33.0µg of 1' and 75µg of 2', 33.0µg of 1' and 100µg of 2', 33.0µg of 1' and 200µg of 2', 49.5µg of 1' and 12.5µg of 2', 49.5µg of 1' and 25µg of 2', 49.5µg of 1' and 50µg of 2', 49.5µg of 1' and 75µg of 2', 49.5µg of 1' and 100µg of 2', 49.5µg of 1' and 200µg of 2', 82.6µg of 1' and 12.5µg of 2', 82.6µg of 1' and 25µg of 2', 82.6µg of 1' and 50µg of 2', 82.6µg of 1' and 75µg of 2', 82.6µg of 1' and 100µg of 2', 82.6µg of 1' and 200µg of 2', 165.1µg of 1' and 12.5µg of 2', 165.1µg of 1' and 25µg of 2', 165.1µg of 1' and 50µg of 2', 165.1µg of 1' and 75µg of 2', 165.1µg of 1' and 100µg of 2', 165.1µg of 1' and 200µg of 2', 206.4µg of 1' and 12.5µg of 2', 206.4µg of 1' and 25µg of 2', 206.4µg of 1' and 50µg of 2', 206.4µg of 1' and 75µg of 2', 206.4µg of 1' and 100µg of 2', 206.4µg of 1' and 200µg of 2', 412.8µg of 1' and 12.5µg of 2', 412.8µg of 1' and 25µg of 2', 412.8µg of 1' and 50µg of 2', 412.8µg of 1' and 75µg of 2', 412.8µg of 1' and 100µg of 2', 412.8µg of 1' and 200µg of 2' are present, for example.

If a combination of active substances wherein the bromide is used as the salt 1 and 2 denotes salmeterol xinafoate is used as the preferred combination of 1 and 2, the amounts of active substances 1' and 2' administered per single dose as specified hereinbefore correspond to the following

amounts of 1 and 2 administered per single dose: 10µg of 1 and 18.2µg of 2, 10µg of 1 and 36.3µg of 2, 10µg of 1 and 72.6µg of 2, 10µg of 1 and 108.9µg of 2, 10µg of 1 and 145.2µg of 2, 10µg of 1 and 290.4µg of 2, 20µg of 1 and 18.2µg of 2, 20µg of 1 and 36.3µg of 2, 20µg of 1 and 72.6µg of 2, 20µg of 1 and 108.9µg of 2, 20µg of 1 and 145.2µg of 2, 20µg of 1 and 290.4µg of 2, 40µg of 1 and 18.2µg of 2, 40µg of 1 and 36.3µg of 2, 40µg of 1 and 72.6µg of 2, 40µg of 1 and 108.9µg of 2, 40µg of 1 and 145.2µg of 2, 40µg of 1 and 290.4µg of 2, 60µg of 1 and 18.2µg of 2, 60µg of 1 and 36.3µg of 2, 60µg of 1 and 72.6µg of 2, 60µg of 1 and 108.9µg of 2, 60µg of 1 and 145.2µg of 2, 60µg of 1 and 290.4µg of 2, 100µg of 1 and 18.2µg of 2, 100µg of 1 and 36.3µg of 2, 100µg of 1 and 72.6µg of 2, 100µg of 1 and 108.9µg of 2, 100µg of 1 and 145.2µg of 2, 100µg of 1 and 290.4µg of 2, 200µg of 1 and 18.2µg of 2, 200µg of 1 and 36.3µg of 2, 200µg of 1 and 72.6µg of 2, 200µg of 1 and 108.9µg of 2, 200µg of 1 and 145.2µg of 2, 200µg of 1 and 290.4µg of 2, 250µg of 1 and 18.2µg of 2, 250µg of 1 and 36.3µg of 2, 250µg of 1 and 72.6µg of 2, 250µg of 1 and 108.9µg of 2, 250µg of 1 and 145.2µg of 2, 250µg of 1 and 290.4µg of 2, 500µg of 1 and 18.2µg of 2, 500µg of 1 and 36.3µg of 2, 500µg of 1 and 72.6µg of 2, 500µg of 1 and 108.9µg of 2, 500µg of 1 and 145.2µg of 2, 500µg of 1 and 290.4µg of 2.

The quantities of active substance in the pharmaceutical combinations which can be administered per single dose can be calculated analogously if instead of the salmeterol xinafoate the compounds 2 salmeterol-4-phenylcinnamic acid salt (4-phenylcinnamate) and salmeterol-5-(2,4-difluorophenyl)salicylic acid salt (5-(2,4-difluorophenyl)salicylate) which are also preferably used according to the invention are used.

The combinations of active substances may contain 1' and 2aa' in weight ratios which are in the range from about 1:30 to 400:1, preferably 1:25 to 200:1, preferably 1:20 to 100:1, more preferably from 1:15 to 50:1.

For example, and without restricting the scope of the invention thereto, preferred combinations of 1 and 2 may contain the cation 1' and the compound 2aa' in the following ratios by weight: 1:15, 1:14, 1:13, 1:12, 1:11, 1:10, 1:9, 1:8, 1:7, 1:6, 1:5, 1:4, 1:3, 1:2, 1:1, 2:1, 3:1, 4:1, 5:1, 6:1, 7:1, 8:1, 9:1,

10:1, 11:1, 12:1, 13:1, 14:1, 15:1, 16:1, 17:1, 18:1, 19:1, 20:1, 21:1, 22:1, 23:1, 24:1, 25:1, 26:1, 27:1, 28:1, 29:1, 30:1, 31:1, 32:1, 33:1, 34:1, 35:1.

The pharmaceutical compositions containing the combinations of 1 and 2 are usually administered so that each single dose contains the cation 1' and the compound 2aa' together in doses of from 5 to 5000µg, preferably from 10 to 2000µg, more preferably from 15 to 1000µg, even more preferably from 20 to 800µg, preferably, from 30 to 750µg, preferably from 40 to 700µg.

For example, combinations of 1 and 2 contain an amount of 1' and 2aa' such that the total dosage per single dose is about 15µg, 20µg, 25µg, 30µg, 35µg, 40µg, 45µg, 50µg, 55µg, 60µg, 65µg, 70µg, 75µg, 80µg, 85µg, 90µg, 95µg, 100µg, 105µg, 110µg, 115µg, 120µg, 125µg, 130µg, 135µg, 140µg, 145µg, 150µg, 155µg, 160µg, 165µg, 170µg, 175µg, 180µg, 185µg, 190µg, 195µg, 200µg, 205µg, 210µg, 215µg, 220µg, 225µg, 230µg, 235µg, 240µg, 245µg, 250µg, 255µg, 260µg, 265µg, 270µg, 275µg, 280µg, 285µg, 290µg, 295µg, 300µg, 305µg, 310µg, 315µg, 320µg, 325µg, 330µg, 335µg, 340µg, 345µg, 350µg, 355µg, 360µg, 365µg, 370µg, 375µg, 380µg, 385µg, 390µg, 395µg, 400µg, 405µg, 410µg, 415µg, 420µg, 425µg, 430µg, 435µg, 440µg, 445µg, 450µg, 455µg, 460µg, 465µg, 470µg, 475µg, 480µg, 485µg, 490µg, 495µg, 500µg, 505µg, 510µg, 515µg, 520µg, 525µg, 530µg, 535µg, 540µg, 545µg, 550µg, 555µg, 560µg, 565µg, 570µg, 575µg, 580µg, 585µg, 590µg, 595µg, 600µg, 605µg, 610µg, 615µg, 620µg, 625µg, 630µg, 635µg, 640µg, 645µg, 650µg, 655µg, 660µg, 665µg, 670µg, 675µg, 680µg, 685µg, 690µg, 695µg, 700µg or similar. It is clear to anyone skilled in the art that the suggested dosages per single dose specified above are not to be regarded as being limited to the numerical values actually stated. Fluctuations of about ± 2.5 µg, particularly in the decimal range, are also included, as will be apparent to the skilled man. In these dosage ranges, the active substances 1' and 2aa' may be present in the weight ratios given above.

For example, and without restricting the scope of the invention thereto, the combinations of 1 and 2 may contain an amount of cation 1' and 2aa' such that each single dose contains, for example, 8.3µg of 1'

and 12.5µg of 2aa', 8.3µg of 1' and 25µg of 2aa', 8.3µg of 1' and 50µg of 2aa',
 8.3µg of 1' and 75µg of 2aa', 8.3µg of 1' and 100µg of 2aa', 8.3µg of 1' and 200µg
 of 2aa', 16.5µg of 1' and 12.5µg of 2aa', 16.5µg of 1' and 25µg of 2aa', 16.5µg of
1' and 50µg of 2aa', 16.5µg of 1' and 75µg of 2aa', 16.5µg of 1' and 100µg of 2aa',
 5 16.5µg of 1' and 200µg of 2aa', 33.0µg of 1' and 12.5µg of 2aa', 33.0µg of 1' and
 25µg of 2aa', 33.0µg of 1' and 50µg of 2aa', 33.0µg of 1' and 75µg of 2aa', 33.0µg
 of 1' and 100µg of 2aa', 33.0µg of 1' and 200µg of 2aa', 49.5µg of 1' and 12.5µg of
2aa', 49.5µg of 1' and 25µg of 2aa', 49.5µg of 1' and 50µg of 2aa', 49.5µg of 1'
 and 75µg of 2aa', 49.5µg of 1' and 100µg of 2aa', 49.5µg of 1' and 200µg of 2aa',
 10 82.6µg of 1' and 12.5µg of 2aa', 82.6µg of 1' and 25µg of 2aa', 82.6µg of 1' and
 50µg of 2aa', 82.6µg of 1' and 75µg of 2aa', 82.6µg of 1' and 100µg of 2aa',
 82.6µg of 1' and 200µg of 2aa', 165.1µg of 1' and 12.5µg of 2aa', 165.1µg of 1'
 and 25µg of 2aa', 165.1µg of 1' and 50µg of 2aa', 165.1µg of 1' and 75µg of 2aa',
 165.1µg of 1' and 100µg of 2aa', 165.1µg of 1' and 200µg of 2aa', 206.4µg of 1'
 15 and 12.5µg of 2aa', 206.4µg of 1' and 25µg of 2aa', 206.4µg of 1' and 50µg of
2aa', 206.4µg of 1' and 75µg of 2aa', 206.4µg of 1' and 100µg of 2aa', 206.4µg of
1' and 200µg of 2aa', 412.8µg of 1' and 12.5µg of 2aa', 412.8µg of 1' and 25µg of
2aa', 412.8µg of 1' and 50µg of 2aa', 412.8µg of 1' and 75µg of 2aa', 412.8µg of 1'
 and 100µg of 2aa', 412.8µg of 1' and 200µg of 2aa'.

20 If the active substance combination wherein the salt 1 is the bromide and the salt
2aa is the maleate of the compound 2aa' is used as the preferred combination of 1
 and 2, the quantities of active substances 1' and 2aa'

administered per single dose as specified above by way of example correspond to
 25 the following amounts of 1 and 2aa administered per single dose:

10µg of 1 and 16.2µg of 2aa, 10µg of 1 and 32.4µg of 2aa, 10µg of 1 and 64.8µg
 of 2aa, 10µg of 1 and 97.2µg of 2aa, 10µg of 1 and 129.6µg of 2aa, 10µg of 1 and
 259.2µg of 2aa, 20µg of 1 and 16.2µg of 2aa, 20µg of 1 and 32.4µg of 2aa, 20µg
 of 1 and 64.8µg of 2aa, 20µg of 1 and 97.2µg of 2aa, 20µg of 1 and 129.6µg of
 30 2aa, 20µg of 1 and 259.2µg of 2aa, 40µg of 1 and 16.2µg of 2aa,
 40µg of 1 and 32.4µg of 2aa, 40µg of 1 and 64.8µg of 2aa, 40µg of 1 and 97.2µg
 of 2aa, 40µg of 1 and 129.6µg of 2aa, 40µg of 1 and 259.2µg of 2aa, 60µg of 1
 and 16.2µg of 2aa, 60µg of 1 and 32.4µg of 2aa, 60µg of 1 and 64.8µg of 2aa,
 60µg of 1 and 97.2µg of 2aa, 60µg of 1 and 129.6µg of 2aa, 60µg of 1 and
 35 259.2µg of 2aa, 100µg of 1 and 16.2µg of 2aa, 100µg of 1 and 32.4µg of 2aa,

100µg of 1 and 64.8µg of 2aa, 100µg of 1 and 97.2µg of 2aa, 100µg of 1 and 129.6µg of 2aa, 100µg of 1 and 259.2µg of 2aa, 200µg of 1 and 16.2µg of 2aa, 200µg of 1 and 32.4µg of 2aa, 200µg of 1 and 64.8µg of 2aa, 200µg of 1 and 97.2µg of 2aa, 200µg of 1 and 129.6µg of 2aa, 200µg of 1 and 259.2µg of 2aa, 250µg of 1 and 16.2µg of 2aa, 250µg of 1 and 32.4µg of 2aa, 250µg of 1 and 64.8µg of 2aa, 250µg of 1 and 97.2µg of 2aa, 250µg of 1 and 129.6µg of 2aa, 250µg of 1 and 259.2µg of 2aa, 500µg of 1 and 16.2µg of 2aa, 500µg of 1 and 32.4µg of 2aa, 500µg of 1 and 64.8µg of 2aa, 500µg of 1 and 97.2µg of 2aa, 500µg of 1 and 129.6µg of 2aa, 500µg of 1 and 259.2µg of 2aa.

The active substance combinations of 1 and 2 are preferably administered by inhalation. For this purpose, ingredients 1 and 2 have to be made available in forms suitable for inhalation. Inhalable preparations disclosed include inhalable powders, propellant-containing metered dose aerosols or propellant-free inhalable solutions. Inhalable powders containing the combination of active substances 1 and 2 may consist of the active substances on their own or of a mixture of the active substances with physiologically acceptable excipients. The term carrier may optionally be used instead of the term excipient. The term propellant-free inhalable solutions may also include concentrates or sterile inhalable solutions ready for use. The preparations may contain the combination of active substances 1 and 2 either together in one formulation or in two separate formulations. These formulations are described in more detail in the next part of the specification.

A) Inhalable powder containing the combinations of active substances 1 and 2 according to the invention:

The inhalable powders may contain 1 and 2 either on their own or in admixture with suitable physiologically acceptable excipients.

If the active substances 1 and 2 are present in admixture with physiologically acceptable excipients, the following physiologically acceptable excipients may be used to prepare these inhalable powders :

monosaccharides (e.g. glucose or arabinose), disaccharides (e.g. lactose,

saccharose, maltose), oligo- and polysaccharides (e.g. dextran), polyalcohols (e.g. sorbitol, mannitol, xylitol), salts (e.g. sodium chloride, calcium carbonate) or mixtures of these excipients with one another. Preferably, mono- or disaccharides are used, while the use of lactose or glucose is preferred, particularly, but not exclusively, in the form of their hydrates.

Disclosed are the inhalable powders wherein the excipients have a maximum average particle size of up to 250µm, preferably between 10 and 150µm, most preferably between 15 and 80µm. It may sometimes seem appropriate to add finer excipient fractions with an average particle size of 1 to 9µm to the excipient mentioned above. These finer excipients are also selected from the group of possible excipients listed hereinbefore. Finally, in order to prepare the inhalable powders, micronised active substance 1 and 2, preferably with an average particle size of 0.5 to 10µm, more preferably from 1 to 6µm, is added to the excipient mixture. Processes for producing the inhalable powders by grinding and micronising and by finally mixing the ingredients together are known from the prior art. The inhalable powders may be prepared and administered either in the form of a single powder mixture which contains both 1 and 2 or in the form of separate inhalable powders which contain only 1 or 2.

The inhalable powders may be administered using inhalers known from the prior art. Inhalable powders which contain one or more physiologically acceptable excipients in addition to 1 and 2 may be administered, for example, by means of inhalers which deliver a single dose from a supply using a measuring chamber as described in US 4570630A, or by other means as described in DE 36 25 685 A. The inhalable powders which contain 1 and 2 optionally in conjunction with a physiologically acceptable excipient may be administered, for example, using the inhaler known by the name Turbuhaler® or using inhalers as disclosed for example in EP 237507 A. Preferably, the inhalable powders according to the invention which contain physiologically acceptable excipient in addition to 1 and 2 are packed into capsules (to produce so-called inhalettes) which are used in inhalers as described, for example, in WO 94/28958.

A particularly preferred inhaler for using the pharmaceutical combination according to the invention in inhalettes is shown in Figure 1.

5 This inhaler (Handyhaler) for inhaling powdered pharmaceutical compositions from capsules is characterised by a housing 1 containing two windows 2, a deck 3 in which there are air inlet ports and which is provided with a screen 5 secured via a screen housing 4, an inhalation chamber 6 connected to the deck 3 on which there is a push button 9 provided with two sharpened pins 7 and movable counter to a spring 8, and a mouthpiece 12 which is connected to the housing 1, the deck 3 and a cover 11 via a spindle 10 to enable it to be flipped open or shut, as well as
10 airholes 13 for adjusting the flow resistance.

If the inhalable powders are packed into capsules (inhalers) for the preferred use described above, the quantities packed into each capsule should be 1 to 30mg per capsule. These capsules may contain, either together or separately, the doses 1 or 1' and 2 or 2'
15 mentioned hereinbefore for each single dose.

B) Propellant gas-driven inhalation aerosols containing the combinations of active substances 1 and 2:

Inhalation aerosols containing propellant gas according to the invention may contain substances 1 and 2 dissolved in the propellant gas or in dispersed form. 1 and 2 may be present in separate formulations or in a single preparation, in which
20 1 and 2 are either both dissolved, both dispersed or only one component is dissolved and the other is dispersed. The propellant gases which may be used to prepare the inhalation aerosols according to the invention are known from the prior art. Suitable propellant gases are selected from among hydrocarbons such as
25 n-propane, n-butane or isobutane and halohydrocarbons such as fluorinated derivatives of methane, ethane, propane, butane, cyclopropane or cyclobutane. The propellant gases mentioned above may be used on their own or in mixtures thereof. Particularly preferred propellant gases are halogenated alkane derivatives selected from TG11, TG12, TG134a (1,1,1,2-tetrafluoroethane) and
30 TG227 (1,1,1,2,3,3,3-heptafluoropropane) and mixtures thereof, of which the propellant gases TG134a, TG227 and mixtures thereof are preferred.

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The propellant-driven inhalation aerosols may also contain other ingredients such as co-solvents, stabilisers, surfactants, antioxidants, lubricants and pH adjusters. All these ingredients are known in the art.

The inhalation aerosols containing propellant gas may contain up to 5 wt.-% of active substance 1 and/or 2. Aerosols according to the invention contain, for example, 0.002 to 5 wt.-%, 0.01 to 3 wt.-%, 0.015 to 2 wt.-%, 0.1 to 2 wt.-%, 0.5 to 2 wt.-% or 0.5 to 1 wt.-% of active substance 1 and/or 2.

If the active substances 1 and/or 2 are present in dispersed form, the particles of active substance preferably have an average particle size of up to 10 μ m, preferably from 0.1 to 6 μ m, more preferably from 1 to 5 μ m.

The propellant-driven inhalation aerosols mentioned above may be administered using inhalers known in the art (MDIs = metered dose inhalers). Accordingly, disclosed are pharmaceutical compositions in the form of propellant-driven aerosols as hereinbefore described combined with one or more inhalers suitable for administering these aerosols. In addition, disclosed are inhalers which are characterised in that they contain the propellant gas-containing aerosols described above. Disclosed further are cartridges fitted with a suitable valve which can be used in a suitable inhaler and which contain one of the above-mentioned propellant gas-containing inhalation aerosols. Suitable cartridges and methods of filling these cartridges with the inhalable aerosols containing propellant gas are known from the prior art.

C) Propellant-free inhalable solutions or suspensions containing the combinations of active substances 1 and 2 according to the invention:

Propellant-free inhalable solutions and suspensions contain, for example, aqueous or alcoholic, preferably ethanolic solvents, optionally ethanolic solvents mixed with aqueous solvents. If aqueous/ethanolic solvent mixtures are used the relative proportion of ethanol compared with water is not limited but preferably the maximum is up to 70 percent by volume, more

particularly up to 60 percent by volume of ethanol. The remainder of the volume is made up of water. The solutions or suspensions containing 1 and 2, separately or together, are adjusted to a pH of 2 to 7, preferably 2 to 5, using suitable acids. The pH may be adjusted using acids selected from inorganic or organic acids. Examples of particularly suitable inorganic acids include hydrochloric acid, hydrobromic acid, nitric acid, sulphuric acid and/or phosphoric acid. Examples of particularly suitable organic acids include ascorbic acid, citric acid, malic acid, tartaric acid, maleic acid, succinic acid, fumaric acid, acetic acid, formic acid and/or propionic acid etc. Preferred inorganic acids are hydrochloric and sulphuric acids. It is also possible to use the acids which have already formed an acid addition salt with one of the active substances. Of the organic acids, ascorbic acid, fumaric acid and citric acid are preferred. If desired, mixtures of the above acids may be used, particularly in the case of acids which have other properties in addition to their acidifying qualities, e.g. as flavourings, antioxidants or complexing agents, such as citric acid or ascorbic acid, for example. It is particularly preferred to use hydrochloric acid to adjust the pH.

The addition of editic acid (EDTA) or one of the known salts thereof, sodium editate, as stabiliser or complexing agent is unnecessary in the present formulation. Other embodiments may contain this compound or these compounds. In a preferred embodiment the content based on sodium editate is less than 100mg/100ml, preferably less than 50mg/100 ml, more preferably less than 20mg/100 ml. Generally, inhalable solutions in which the content of sodium editate is from 0 to 10mg/100ml are preferred.

Co-solvents and/or other excipients may be added to the propellant-free inhalable solutions. Preferred co-solvents are those which contain hydroxyl groups or other polar groups, e.g. alcohols - particularly isopropyl alcohol, glycols - particularly propyleneglycol, polyethyleneglycol, polypropyleneglycol, glycolether, glycerol, polyoxyethylene alcohols and polyoxyethylene fatty acid esters. The terms excipients and additives in this context denote any pharmacologically acceptable substance which is not an active substance but which can be formulated with the active substance or substances in the pharmacologically suitable solvent in order to improve the qualitative properties of the active substance formulation. Preferably, these substances have

no pharmacological effect or, in connection with the desired therapy, no appreciable or at least no undesirable pharmacological effect. The excipients and additives include, for example, surfactants such as soya lecithin, oleic acid, sorbitan esters, such as polysorbates, polyvinylpyrrolidone, other stabilisers, complexing agents, antioxidants and/or preservatives which guarantee or prolong the shelf life of the finished pharmaceutical formulation, flavourings, vitamins and/or other additives known in the art. The additives also include pharmacologically acceptable salts such as sodium chloride as isotonic agents.

The preferred excipients include antioxidants such as ascorbic acid, for example, provided that it has not already been used to adjust the pH, vitamin A, vitamin E, tocopherols and similar vitamins and provitamins occurring in the human body.

Preservatives may be used to protect the formulation from contamination with pathogens. Suitable preservatives are those which are known in the art, particularly cetyl pyridinium chloride, benzalkonium chloride or benzoic acid or benzoates such as sodium benzoate in the concentration known from the prior art. The preservatives mentioned above are preferably present in concentrations of up to 50mg/100ml, more preferably between 5 and 20mg/100ml.

Preferred formulations contain, in addition to the solvent water and the combination of active substances 1 and 2, only benzalkonium chloride and sodium editate. In another preferred embodiment, no sodium editate is present.

The propellant-free inhalable solutions disclosed can be administered in particular using inhalers of the kind which are capable of nebulising a small amount of a liquid formulation in the therapeutic dose within a few seconds to produce an aerosol suitable for therapeutic inhalation. Preferred inhalers are those in which a quantity of less than

100 μ L, preferably less than 50 μ L, more preferably between 20 and 30 μ L of active substance solution can be nebulised in preferably one spray action to form an aerosol with an average particle size of less than 20 μ m, preferably less than 10 μ m, in such a way that the inhalable part of the aerosol corresponds to the therapeutically effective quantity.

An apparatus of this kind for propellant-free delivery of a metered quantity of a liquid pharmaceutical composition for inhalation is described for example in International Patent Application WO 91/14468 and also in WO 97/12687 (cf. in particular Figures 6a and 6b). The nebulisers (devices) described therein are
5 known by the name Respimat®.

This nebuliser (Respimat®) can advantageously be used to produce the inhalable aerosols disclosed containing the combination of active substances 1 and 2. Because of its cylindrical shape and handy size of less than 9 to 15 cm long and 2 to 4 cm wide, this device can be carried at all times by the
10 patient. The nebuliser sprays a defined volume of pharmaceutical formulation using high pressures through small nozzles so as to produce inhalable aerosols.

The preferred atomiser essentially consists of an upper housing part, a pump housing, a nozzle, a locking mechanism, a spring housing, a spring and a storage container, characterised by

- 15 - a pump housing which is secured in the upper housing part and which comprises at one end a nozzle body with the nozzle or nozzle arrangement,
- a hollow plunger with valve body,
- a power takeoff flange in which the hollow plunger is secured and which is located in the upper housing part,
- 20 - a locking mechanism situated in the upper housing part,
- a spring housing with the spring contained therein, which is rotatably mounted on the upper housing part by means of a rotary bearing,
- a lower housing part which is fitted onto the spring housing in the axial direction.

25 The hollow plunger with valve body corresponds to a device disclosed in WO 97/12687. It projects partially into the cylinder of the pump housing and is axially movable within the cylinder. Reference is made in particular to Figures 1 to 4, especially Figure 3, and the relevant parts of the description. The hollow
30 plunger with valve body exerts a pressure of 5 to 60 Mpa (about 50 to 600 bar), preferably 10 to 60 Mpa (about 100 to 600 bar) on the fluid, the measured amount of active substance solution, at its high pressure end at the moment when the spring is actuated. Volumes of 10 to 50 microlitres are preferred, while volumes of

10 to 20 microlitres are particularly preferred and a volume of 15 microlitres per spray is most particularly preferred.

5 The valve body is preferably mounted at the end of the hollow plunger facing the valve body.

10 The nozzle in the nozzle body is preferably microstructured, i.e. produced by microtechnology. Microstructured nozzle bodies are disclosed for example in WO-94/07607; reference is hereby made to the contents of this specification, particularly Figure 1 therein and the associated description.

15 The nozzle body consists for example of two sheets of glass and/or silicon firmly joined together, at least one of which has one or more microstructured channels which connect the nozzle inlet end to the nozzle outlet end. At the nozzle outlet end there is at least one round or non-round opening 2 to 10 microns deep and 5 to 15 microns wide, the depth preferably being 4.5 to 6.5 microns while the length is preferably 7 to 9 microns.

20 In the case of a plurality of nozzle openings, preferably two, the directions of spraying of the nozzles in the nozzle body may extend parallel to one another or may be inclined relative to one another in the direction of the nozzle opening. In a nozzle body with at least two nozzle openings at the outlet end the directions of spraying may be at an angle of 20 to 160° to one another, preferably 60 to 150°, most preferably 80 to 100°. The nozzle openings are preferably arranged at a spacing of 10 to 200 microns, more preferably at a spacing of 10 to 100 microns, most preferably 30 to 70 microns. Spacings of 50 microns are most preferred.

25 The directions of spraying will therefore meet in the vicinity of the nozzle openings.

30 The liquid pharmaceutical preparation strikes the nozzle body with an entry pressure of up to 600 bar, preferably 200 to 300 bar, and is atomised into an inhalable aerosol through the nozzle openings. The preferred particle or droplet sizes of the aerosol are up to 20 microns, preferably 3 to 10 microns.

The locking mechanism contains a spring, preferably a cylindrical helical compression spring, as a store for the mechanical energy. The spring acts on the power takeoff flange as an actuating member the movement of which is

determined by the position of a locking member. The travel of the power takeoff flange is precisely limited by an upper and lower stop. The spring is preferably biased, via a power step-up gear, e.g. a helical thrust gear, by an external torque which is produced when the upper housing part is rotated counter to the spring housing in the lower housing part. In this case, the upper housing part and the power takeoff flange have a single or multiple V-shaped gear.

The locking member with engaging locking surfaces is arranged in a ring around the power takeoff flange. It consists, for example, of a ring of plastic or metal which is inherently radially elastically deformable. The ring is arranged in a plane at right angles to the atomiser axis. After the biasing of the spring, the locking surfaces of the locking member move into the path of the power takeoff flange and prevent the spring from relaxing. The locking member is actuated by means of a button. The actuating button is connected or coupled to the locking member. In order to actuate the locking mechanism, the actuating button is moved parallel to the annular plane, preferably into the atomiser; this causes the deformable ring to deform in the annular plane. Details of the construction of the locking mechanism are given in WO 97/20590.

The lower housing part is pushed axially over the spring housing and covers the mounting, the drive of the spindle and the storage container for the fluid.

When the atomiser is actuated the upper housing part is rotated relative to the lower housing part, the lower housing part taking the spring housing with it. The spring is thereby compressed and biased by means of the helical thrust gear and the locking mechanism engages automatically. The angle of rotation is preferably a whole-number fraction of 360 degrees, e.g. 180 degrees. At the same time as the spring is biased, the power takeoff part in the upper housing part is moved along by a given distance, the hollow plunger is withdrawn inside the cylinder in the pump housing, as a result of which some of the fluid is sucked out of the storage container and into the high pressure chamber in front of the nozzle.

If desired, a number of exchangeable storage containers which contain the fluid to be atomised may be pushed into the atomiser one after another and used in

succession. The storage container contains the aqueous aerosol preparation according to the invention.

The atomising process is initiated by pressing gently on the actuating button. As a result, the locking mechanism opens up the path for the power takeoff member. The biased spring pushes the plunger into the cylinder of the pump housing. The fluid leaves the nozzle of the atomiser in atomised form.

Further details of construction are disclosed in PCT Applications WO 97/12683 and WO 97/20590, to which reference is hereby made.

The components of the atomiser (nebuliser) are made of a material which is suitable for its purpose. The housing of the atomiser and, if its operation permits, other parts as well, are preferably made of plastics, e.g. by injection moulding. For medicinal purposes, physiologically safe materials are used.

Figures 2a/b attached to this patent application, which are identical to Figures 6a/b of WO 97/12687, show the nebuliser (Respimat®) which can be used for inhaling the aqueous aerosol preparations as disclosed herein.

Figure 2a shows a longitudinal section through the atomiser with the spring biased while Figure 2b shows a longitudinal section through the atomiser with the spring relaxed.

The upper housing part (51) contains the pump housing (52) on the end of which is mounted the holder (53) for the atomiser nozzle. In the holder is the nozzle body (54) and a filter (55). The hollow plunger (57) fixed in the power takeoff flange (56) of the locking mechanism projects partially into the cylinder of the pump housing. At its end the hollow plunger carries the valve body (58). The hollow plunger is sealed off by means of the seal (59). Inside the upper housing part is the stop (60) on which the power takeoff flange abuts when the spring is relaxed. On the power takeoff flange is the stop (61) on which the power takeoff flange abuts when the spring is biased. After the biasing of the spring the locking member (62) moves between the stop (61) and a support (63) in the upper housing part. The actuating button (64) is connected to the locking member. The

upper housing part ends in the mouthpiece (65) and is sealed off by means of the protective cover (66) which can be placed thereon.

The spring housing (67) with compression spring (68) is rotatably mounted on the upper housing part by means of the snap-in lugs (69) and rotary bearing. The lower housing part (70) is pushed over the spring housing. Inside the spring housing is the exchangeable storage container (71) for the fluid (72) which is to be atomised. The storage container is sealed off by the stopper (73) through which the hollow plunger projects into the storage container and is immersed at its end in the fluid (supply of active substance solution).

The spindle (74) for the mechanical counter is mounted in the covering of the spring housing. At the end of the spindle facing the upper housing part is the drive pinion (75). The slider (76) sits on the spindle.

The nebuliser described above is suitable for nebulising the aerosol preparations according to the invention to produce an aerosol suitable for inhalation.

If the formulation according to the invention is nebulised using the method described above (Respimat®) the quantity delivered should correspond to a defined quantity with a tolerance of not more than 25%, preferably 20% of this amount in at least 97%, preferably at least 98% of all operations of the inhaler (spray actuations). Preferably, between 5 and 30 mg of formulation, most preferably between 5 and 20 mg of formulation are delivered as a defined mass on each actuation.

However, the formulation as disclosed may also be nebulised by means of inhalers other than those described above, e.g. jet stream inhalers or other stationary nebulisers.

Accordingly, disclosed herein are pharmaceutical formulations in the form of propellant-free inhalable solutions or suspensions as described above combined with a device suitable for administering these formulations, preferably in conjunction with the Respimat®. Preferably, one embodiment relates to propellant-free inhalable solutions or suspensions

12 October 2006

characterised by the combination of active substances 1 and 2 in conjunction with the device known by the name Respimat®. In addition, disclosed herein are the above-mentioned devices for inhalation, preferably the Respimat®, characterized in that they contain the propellant-free inhalable solutions and suspensions described hereinbefore.

Inhalable solutions which contain the active substances 1 and 2 in a single preparation are preferred. The term "single preparation" also includes preparations which contain the two ingredients 1 and 2 in two-chamber cartridges, as disclosed for example in WO 00/23037. Reference is hereby made to this publication in its entirety.

The propellant-free inhalable solutions or suspensions disclosed may take the form of concentrates or sterile inhalable solutions or suspensions ready for use, as well as the above-mentioned solutions and suspensions designed for use in a Respimat®. Formulations ready for use may be produced from the concentrates, for example, by the addition of isotonic saline solutions. Sterile formulations ready for use may be administered using energy-operated free-standing or portable nebulisers which produce inhalable aerosols by means of ultrasound or compressed air by the Venturi principle or other principles.

Accordingly, disclosed are pharmaceutical compositions in the form of propellant-free inhalable solutions or suspensions as described hereinbefore which take the form of concentrates or sterile formulations ready for use, combined with a device suitable for administering these solutions, characterised in that the device is an energy-operated free-standing or portable nebuliser which produces inhalable aerosols by means of ultrasound or compressed air by the Venturi principle or other methods.

The Examples which follow serve to illustrate the present invention in more detail without restricting the scope of the invention to the following embodiments by way of example.

First, the preparation of compounds 1 and 2 used within the scope of the present invention which are not known in the art will be described.

1) Preparation of the compounds of formula 1:

5 **1.a.: 2,2-Diphenylpropionic acid chloride:**

52.08g (0.33 mol) of oxalyl chloride are slowly added dropwise at 20°C to a suspension of 25.0 g (0.11 mol) of 2,2-diphenylpropionic acid, 100 ml of dichloromethane and 4 drops of dimethylformamide. The mixture is stirred for 1 h at 20°C and 0.5 h at 50°C. The solvent is distilled off and the residue remaining is
10 used in the next step without any further purification.

1.b.: scopine 2,2-diphenylpropionate:

The residue obtained from step 1.a. is dissolved in 100 ml of dichloromethane and at 40°C a solution of 51.45 g (0.33 mol) of scopine in 200 ml of dichloromethane is
15 added dropwise thereto. The resulting suspension is stirred for 24 h at 40°C, then the precipitate formed is suction filtered and the filtrate is extracted first with water, then with aqueous hydrochloric acid. The combined aqueous phases are made alkaline with aqueous sodium carbonate solution, extracted with dichloromethane, the organic phase is dried over Na₂SO₄, evaporated to dryness and the
20 hydrochloride is precipitated from the residue. The product is purified by recrystallisation from acetonitrile.

Yield: 20.85 g (= 47 % of theory)

DC: R_f value: 0.24 (eluant: sec. butanol/formic acid/water 75:15:10);

m.p.: 203-204°C.

25 **1.c: scopine 2,2-diphenylpropionate methobromide :**

11.98 g (0.033 mol) of the compound of step 1.b, 210 ml of acetonitrile, 70 ml of dichloromethane and 20.16 g (0.1 mol) of 46.92 % bromomethane in acetonitrile are combined at 20°C and left to stand for 3 days. The solution is evaporated to
30 dryness and the residue is recrystallised from isopropanol.

Yield: 11.34 g (= 75 % of theory); m.p.: 208-209°C.

C₂₄H₂₈NO₃xBr (458.4);

Elemental analysis: calculated: C (62.89) H (6.16) N (3.06)

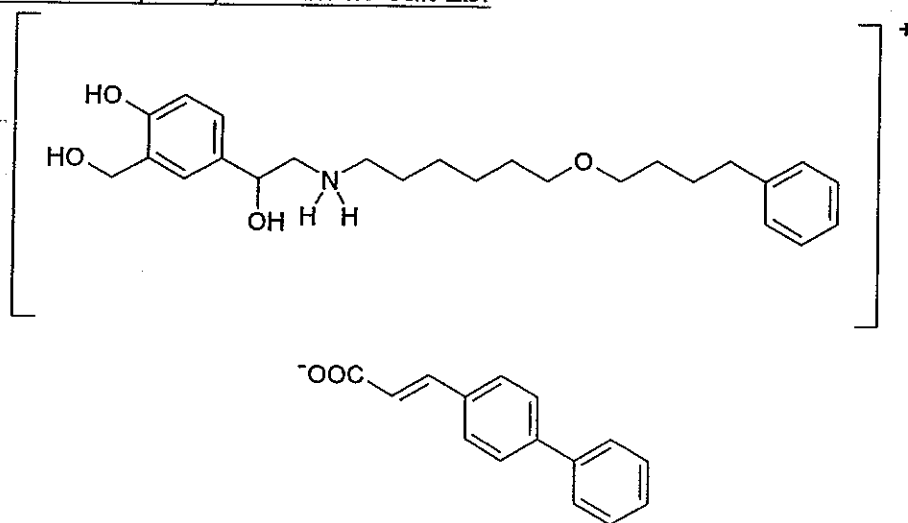
found: C (62.85) H (6.12) N (3.07).

The salts **1** wherein X^- denotes an anion with a single negative charge other than bromide may be obtained in a manner similar to step 1.3.

2.) Preparation of the compounds of formula 2:

5

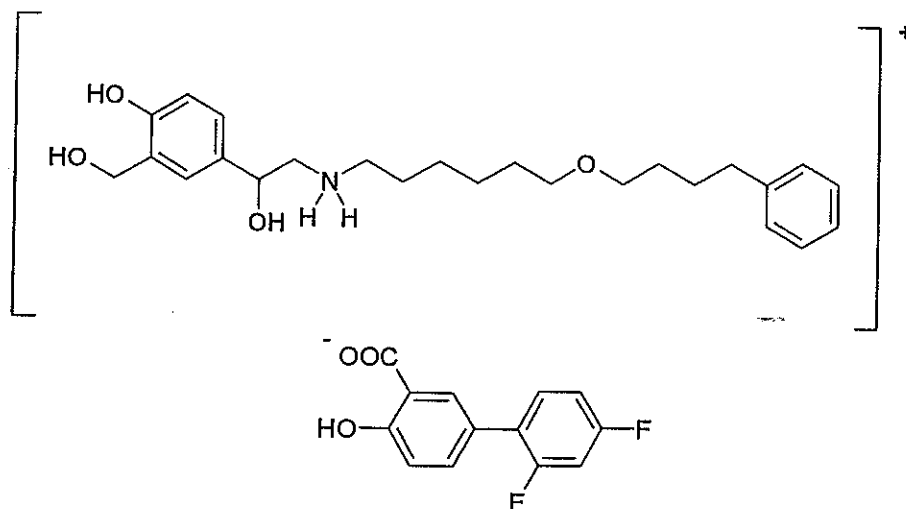
2.1: Salmeterol-4-phenylcinnamate salt **2b**:



1.35 g (6 mmol) of 4-phenylcinnamic acid are dissolved by refluxing in 75 mL of ethyl acetate. To this solution is added a warm solution of 2.5 g (6 mmol) of salmeterol in 25 mL of ethyl acetate. The solution is allowed to cool and stirred for 16 h at room temperature. The suspension is filtered, the precipitate is washed with ethyl acetate and tert.-butylmethylether und dried *in vacuo* at 25-30°C. 47 g of the title compound are obtained as a colourless solid. Melting point: 109°C;

15

2.2.: Salmeterol-5-(2,4-difluorophenyl)salicylate salt 2c:



30 g of salmeterol are dissolved by refluxing in 300 mL of ethyl acetate. 18.3 g of
 5 5-(2,4-difluorophenyl)salicylic acid (Diflunisal) are added to this solution. The
 solution is allowed to cool to ambient temperature. The suspension is filtered off,
 the precipitate is washed with ethyl acetate and dried *in vacuo* at 35°C. 46 g of the
 title salt are obtained as a colourless solid.

Melting point: 104°C

The following examples of formulations, which may be obtained analogously to
 methods known in the art, serve to illustrate the present invention more fully
 without restricting it to the contents of these examples.

Examples of Formulations

A) Inhalable powders:

1)

Ingredients	µg per capsule
<u>1'</u> -bromide	200
Formoterol fumarate dihydrate	12
Lactose	24788
Total	25000

5 2)

Ingredients	µg per capsule
<u>1'</u> -bromide	100
Salmeterol xinafoate	50
Lactose	12350
Total	12500

3)

Ingredients	µg per capsule
<u>1'</u> -bromide	200
Salmeterol xinafoate	50
Lactose	12250
Total	12500

10 4)

Ingredients	µg per capsule
<u>1'</u> -bromide	200
Formoterol fumarate dihydrate	24
Lactose	24776
Total	25000

5)

Ingredients	µg per capsule
<u>1'</u> -bromide	100
<u>2b</u>	50
Lactose	12350
Total	12500

6)

Ingredients	µg per capsule
<u>1'</u> -bromide	200
<u>2c</u>	50
Lactose	12250
Total	12500

5

7)

Ingredients	µg per capsule
<u>1'</u> -bromide	100
<u>2aa'</u> maleate salt	65
Lactose	12335
Total	12500

8)

Ingredients	µg per capsule
<u>1'</u> -bromide	200
<u>2aa'</u> maleate salt	65
Lactose	12235
Total	12500

10

B) Propellant-containing inhalable aerosols:

1) Suspension aerosol:

Ingredients	% by weight
<u>1'</u> -bromide	0.020
Salmeterol xinafoate	0.066
Soya lecithin	0.2
TG 11 : TG12 = 2:3	ad 100

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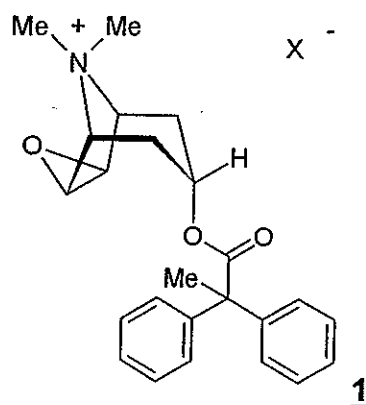
2) Suspension aerosol:

Ingredients	% by weight
<u>1'</u> -bromide	0.039
Salmeterol xinafoate	0.033
Absolute ethanol	0.5
Isopropyl myristate	0.1
TG 227	ad 100

10

Patent Claims

- 1) Pharmaceutical compositions, characterised in that they contain one or
5 more salts of formula 1



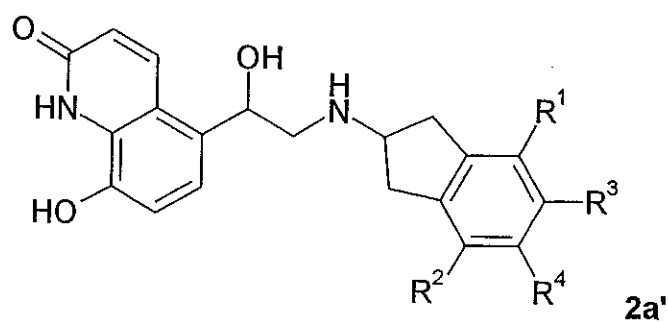
wherein

- 10 X⁻ denotes an anion with a single negative charge, preferably an anion selected from the group consisting of chloride, bromide, iodide, sulphate, phosphate, methanesulphonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate and p-toluenesulphonate,

- 15 combined with one or more betamimetics (2), optionally in the form of the enantiomers, mixtures of the enantiomers or in the form of the racemates thereof, optionally in the form of the solvates or hydrates and optionally together with a pharmaceutically acceptable excipient.

- 20 2) Pharmaceutical composition according to claim 1, characterised in that the active substances 1 and 2 are present either together in a single formulation or in two separate formulations.

- 25 3) Pharmaceutical composition according to claim 1 or 2, characterised in that the betamimetics 2 are salmeterol salts, formoterol salts or acid addition salts of the compounds of formula 2a'



wherein

wherein

- 5 R^1 and R^2 which may be identical or different denote hydrogen or C_1 - C_4 -alkyl;
 R^3 and R^4 which may be identical or different denote hydrogen, C_1 - C_4 -alkyl, -O-
 C_1 - C_4 -alkyl, - C_1 - C_4 -alkylene-O- C_1 - C_4 -alkyl or
 R^3 and R^4 together denote one of the bridging groups
 C_1 - C_4 -alkylene- or -O- C_1 - C_4 -alkylene-O-.

10

- 4) Pharmaceutical compositions according to claim 3, characterised in that
 the compounds 2 are present in the form of the salts of hydrochloric acid,
 hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, acetic
 acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid, 1-hydroxy-2-
 15 naphthalenecarboxylic acid, 4-phenylcinnamic acid, 5-(2,4-difluorophenyl)salicylic
 acid or maleic acid.

- 5) Pharmaceutical compositions according to claim 3 or 4, characterised in that
 the compounds 2 are salmeterol xinafoate, salmeterol-4-phenylcinnamate or
 20 salmeterol-5-(2,4-difluorophenyl)salicylate.

- 6) Pharmaceutical compositions according to claim 3 or 4, characterised in that
 the compounds 2 are salts of the compounds of formula 2a',

wherein

- 25 R^1 and R^2 which may be identical or different denote hydrogen, methyl or ethyl;
 R^3 and R^4 which may be identical or different denote hydrogen, methyl, ethyl,
 propyl, butyl, methoxy, ethoxy, methoxymethyl, or methoxyethyl, or
 R^3 and R^4 together denote one of the bridging groups
 propylene, butylene, -O-ethylene-O- or -O-propylene-O-.

30

7) Pharmaceutical compositions according to claim 3, 4 or 6, characterised in that the compounds 2 are salts of the compounds of formula 2a' wherein

- 5 R^1 and R^2 which may be identical or different denote hydrogen or ethyl;
 R^3 and R^4 which may be identical or different denote hydrogen, methyl, ethyl, propyl, butyl or methoxymethyl or
 R^3 and R^4 together denote one of the bridging groups
 butylene or -O-ethylene-O-.

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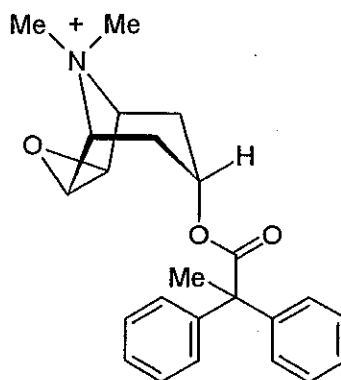
8) Pharmaceutical compositions according to claim 3, 4, 6 or 7, characterised in that the compounds 2 are salts of the compounds of formula 2a' wherein

- a) R^1 and R^2 denote hydrogen and R^3 and R^4 denote ethyl; or
 b) R^1 and R^2 denote hydrogen and R^3 and R^4 denote methyl; or
 15 c) R^1 and R^2 denote ethyl and R^3 and R^4 denote hydrogen; or
 d) R^1 and R^2 denote hydrogen and R^3 and R^4 together denote butylene;
 or
 e) R^1 and R^2 denote hydrogen and R^3 and R^4 together denote -O-ethylene-O-; or
 20 f) R^1 and R^2 denote hydrogen and R^3 and R^4 denote tert.-butyl or
 g) R^1 and R^2 denote hydrogen and R^3 and R^4 denote iso-propyl; or
 h) R^1 and R^2 denote hydrogen and R^3 and R^4 denote methoxymethyl.

20

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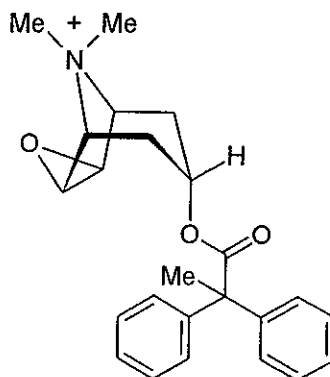
9) Pharmaceutical compositions according to one of claims 3 to 5, characterised in that the weight ratios of 1'



to salmeterol 2' are in a range from about 1:30 to 400:1, preferably 1:25 to 200:1.

10) Pharmaceutical compositions according to one of claims 3 or 4, characterised in that the compounds 2 are formoterol hydrochloride, formoterol sulphate or formoterol fumarate.

- 5 11) Pharmaceutical compositions according to claim 10, characterised in that the weight ratios of 1'



to formoterol 2' are in a range from about 1:10 to 300:1, preferably 1:5 to 200:1.

10

12) Pharmaceutical composition according to one of claims 1 to 11, characterised in that it is in the form of a preparation suitable for inhalation.

- 15 13) Pharmaceutical composition according to claim 12, characterised in that it is a preparation selected from among the inhalable powders, propellant-containing metered-dose aerosols and propellant-free inhalable solutions.

20 14) Pharmaceutical composition according to claim 13, characterised in that it is an inhalable powder which contains 1 and 2 in admixture with suitable physiologically acceptable excipients selected from among the monosaccharides, disaccharides, oligo- and polysaccharides, polyalcohols, salts, or mixtures of these excipients with one another.

- 25 15) Inhalable powder according to claim 14, characterised in that the excipient has a maximum average particle size of up to 250µm, preferably between 10 and 150µm.

- 16) Pharmaceutical composition according to claim 13, characterised in that it is an inhalable powder which contains only the active substances 1 and 2 as its ingredients.
- 5 17) Pharmaceutical composition according to claim 13, characterised in that it is a propellant-containing inhalable aerosol which contains 1 and 2 in dissolved or dispersed form.
- 10 18) Propellant-containing inhalable aerosol according to claim 17, characterised in that it contains, as propellant gas, hydrocarbons such as n-propane, n-butane or isobutane or halohydrocarbons such as chlorinated and/or fluorinated derivatives of methane, ethane, propane, butane, cyclopropane or cyclobutane.
- 15 19) Propellant-containing inhalable aerosol according to claim 18, characterised in that the propellant gas is TG11, TG12, TG134a, TG227 or mixtures thereof, preferably TG134a, TG227 or a mixture thereof.
- 20 20) Propellant-containing inhalable aerosol according to one of claims 17 to 19, characterised in that it may contain up to 5 % by weight of active substance 1' and/or 2'.
- 25 21) Pharmaceutical composition according to claim 13, characterised in that it is a propellant-free inhalable solution which contains water, ethanol or a mixture of water and ethanol as solvent.
- 22) Inhalable solution according to claim 21, characterised in that it optionally contains other co-solvents and/or excipients.
- 30 23) Inhalable solution according to claim 22, characterised in that it contains as co-solvents ingredients which contain hydroxyl groups or other polar groups, e.g. alcohols - particularly isopropyl alcohol, glycols - particularly propyleneglycol, polyethyleneglycol, polypropyleneglycol, glycolether, glycerol, polyoxyethylene alcohols and polyoxyethylene fatty acid esters.

24) Inhalable solutions according to one of claims 22 or 23, characterised in that they contain as excipients surfactants, stabilisers, complexing agents, antioxidants and/or preservatives, flavourings, pharmacologically acceptable salts and/or vitamins.

5

25) Inhalable solutions according to claim 24, characterised in that they contain as complexing agents edetic acid or a salt of edetic acid, preferably sodium edetate.

10

26) Use of a composition according to one of claims 1 to 25 for preparing a medicament for the treatment of inflammatory or obstructive respiratory complaints, particularly asthma or COPD.