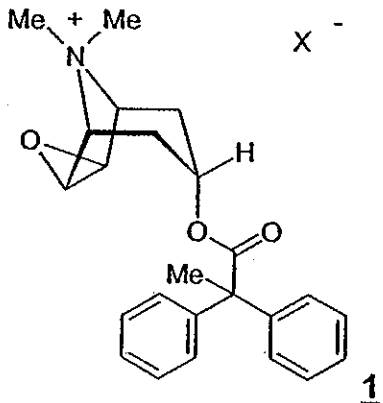
MEDICAMENTS CONTAINING STERIOIDS AND A NOVEL ANTICHOLINESTERASE DRUG

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

Description of the invention

According to a first aspect of the present invention, there is provided pharmaceutical compositions, characterised in that they contain one or more, preferably one, salt of formula **1**



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, preferably one, steroid **2**, optionally in the form of the diastereomers, mixtures of the diastereomers 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.

According to a second aspect, there is provided an inhalable powder which contains formula **1** and steroid **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, characterized in that the excipient has a maximum average particle size of up to 250µm, preferably between 10 and 150µm.

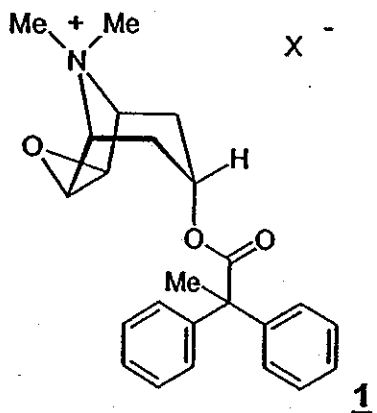
According to a third aspect, there is provided a propellant-containing inhalable aerosol which contains formula 1 and steroid 2 in dissolved or dispersed form, characterized in that it contains, as propellant gas, hydrocarbons such as n-propane, n-butane or isobutene or halohydrocarbons such as chlorinated and/or fluorinated derivatives of methane, ethane, propane, butane, cyclopropane or cyclobutane.

According to a fourth aspect, there is provided an inhalable solution which contains water, ethanol or a mixture of water and ethanol as solvent, characterized in that it optionally contains other co-solvents and/or excipients.

According to a fifth aspect, there is provided a use of a composition as defined above, for preparing a medicament for the treatment of inflammatory and/or obstructive respiratory complaints, particularly asthma or COPD.

Disclosed herein are pharmaceutical compositions based on steroids and salts of an anticholinergic 1, processes for preparing them and their use in the treatment of respiratory complaints.

The anticholinergic agents used are the salts of formula 1



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 scopine, 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 scopine, 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 allows the patient to become accustomed relatively quickly to the regular taking of the medicament at a particular time of the day.

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

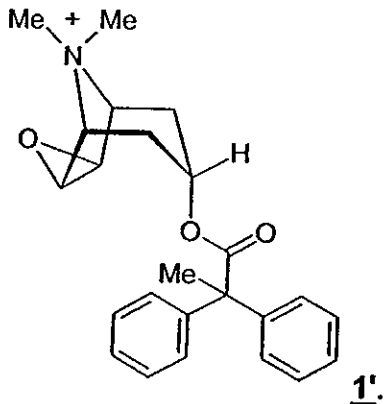
as constant as possible over a fairly lengthy ensuing period. On the other hand the duration of activity of the pharmaceutical composition should not greatly exceed a period of about one day. Ideally, an active substance should have an activity profile such that the preparation of a pharmaceutical composition 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 benzilic acid esters of scopine, 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.

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, preferably one, steroid **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. Furthermore, this reduces unwanted side effects such as may occur when steroids are administered, for example.

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 formulation. The pharmaceutical compositions as disclosed are preferably administered by inhalation.

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** :



1'.

Any reference to compounds 1 naturally also includes a reference to the cation 1'.

In the pharmaceutical combinations mentioned above the active substances1 and 2 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.

The term steroids (hereinafter 2), which are optionally also referred to as corticosteroids, denotes compounds selected from among flunisolide, beclomethasone, triamcinolone, budesonide, fluticasone, mometasone, ciclesonide, rofleponide, ST-126 and dexamethasone. Preferably, the compound 2 is selected from among budesonide, fluticasone, mometasone, ciclesonide and ST-126.

Any reference to steroids 2 disclosed herein includes a reference to the salts or derivatives which may be formed from the steroids. Examples of possible salts or derivatives include: sodium salts, sulphobenzoates, phosphates, isonicotinates, acetates, propionates, dihydrogen phosphates, palmitates, pivalates or furoates. In some cases the compounds of formula 2 may also occur in the form of their hydrates. Any reference to steroids 2 also can include a reference to the compounds 2 in the form of their diastereomers, mixtures of diastereomers or in the form of the racemates.

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

Therapeutically effective quantities of the salts **1** can be used for preparing a pharmaceutical composition also containing steroids **2** for treating inflammatory or obstructive diseases of the respiratory tract. Preferably, disclosed herein is the 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 further is the use of therapeutically effect amounts of salts **1** and steroids **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 as 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 which may be used vary on the basis of the different molecular weights of the various compounds and their different potencies. As a rule, the pharmaceutical combinations as disclosed may contain the cation **1'** and a steroid **2** in ratios by weight ranging from 1:250 to 250:1, preferably from 1:150 to 150:1. In the particularly preferred pharmaceutical combinations which contain in addition to **1'** a compound selected from among the group consisting of budesonide, fluticasone, mometasone, ciclesonide and ST-126 as the steroid **2**, the weight ratios of **1'** to **2** are most preferably in a range from about 1:40 to 40:1, more preferably from 1:30 to 30:1.

For example, preferred combinations of 1 and 2 as disclosed may contain the cation 1' and one of the abovementioned preferred steroids 2 in the following weight ratios: 1:20; 1:19; 1:18; 1:17; 1:16; 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.

The pharmaceutical compositions as disclosed containing the combinations of 1 and 2 are normally administered so that 1' and 2 are present together in doses of 5 to 5000µg, preferably from 10 to 2000µg, more preferably from 15 to 1000µg, better still from 20 to 800µg, preferably, according to the invention, from 30 to 700µg, preferably from 40 to 600µg, preferably from 50 to 550µg, preferably from 40 to 500µg, most preferably 50 to 400µg per single dose. For example, combinations of 1 and 2 according to the invention contain a quantity of 1' and steroid 2 such that the total dosage per single dose is about 35µg, 45µg, 50µg, 55µg, 60µg, 65µg, 70µg, 75µg, 80µg, 85µg, 90µg, 95µg, 100µg, 105µg, 110µg, 115µg, 120µg, 125µg, 130µg, 135µg,140 µg,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 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.

For example, the combinations of 1 and 2 as disclosed may contain a quantity of

cation 1' and steroid 2 such that, for each single dose, 16.5µg of 1' and 25µg of 2, 16.5µg of 1' and 50µg of 2, 16.5µg of 1' and 100µg of 2, 16.5µg of 1' and 150µg of 2, 16.5µg of 1' and 200µg of 2, 16.5µg of 1' and 250µg of 2, 33.0µg of 1' and 25µg of 2, 33.0µg of 1' and 50µg of 2, 33.0µg of 1' and 100µg of 2, 33.0µg of 1' and 150µg of 2, 33.0µg of 1' and 200µg of 2, 33.0µg of 1' and 250µg of 2, 49.5µg of 1' and 25µg of 2, 49.5µg of 1' and 50µg of 2, 49.5µg of 1' and 100µg of 2, 49.5µg of 1' and 150µg of 2, 49.5µg of 1' and 200µg of 2, 49.5µg of 1' and 250µg of 2, 82.6µg of 1' and 25µg of 2, 82.6µg of 1' and 50µg of 2, 82.6µg of 1' and 100µg of 2, 82.6µg of 1' and 150µg of 2, 82.6µg of 1' and 200µg of 2, 82.6µg of 1' and 250µg of 2, 165.1µg of 1' and 25µg of 2, 165.1µg of 1' and 50µg of 2, 165.1µg of 1' and 50µg of 2, 165.1µg of 1' and 100µg of 2, 165.1µg of 1' and 150µg of 2, 165.1µg of 1' and 200µg of 2, 165.1µg of 1' and 250µg of 2, 206.4µg of 1' and 25µg of 2, 206.4µg of 1' and 50µg of 2, 206.4µg of 1' and 100µg of 2, 206.4µg of 1' and 150µg of 2, 206.4µg of 1' and 200µg of 2, 206.4µg of 1' and 250µg of 2, 412.8µg of 1' and 25µg of 2, 412.8µg of 1' and 50µg of 2, 412.8µg of 1' and 100µg of 2, 412.8µg of 1' and 150µg of 2, 412.8µg of 1' and 200µg of 2, 412.8µg of 1' and 250µg of 2 are present.

If the active substance combination in which the bromide is used as the salt 1 and in which 2 denotes one of the steroids mentioned above as being preferred is used as the preferred combination of 1 and 2 disclosed herein, 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:

20µg of 1 and 25µg of 2, 20µg of 1 and 50µg of 2, 20µg of 1 and 100µg of 2, 20µg of 1 and 150µg of 2, 20µg of 1 and 200µg of 2, 20µg of 1 and 250µg of 2, 40µg of 1 and 25µg of 2, 40µg of 1 and 25µg of 2, 40µg of 1 and 50µg of 2, 40µg of 1 and 100µg of 2, 40µg of 1 and 150µg of 2, 40µg of 1 and 200µg of 2, 40µg of 1 and 250µg of 2, 60µg of 1 and 25µg of 2, 60µg of 1 and 50µg of 2, 60µg of 1 and 100µg of 2, 60µg of 1 and 150µg of 2, 60µg of 1 and 200µg of 2, 60µg of 1 and 250µg of 2, 100µg of 1 and 25µg of 2, 100µg of 1 and 50µg of 2, 100µg of 1 and 100µg of 2, 100µg of 1 and 150µg of 2, 100µg of 1 and 200µg of 2, 100µg of 1 and 250µg of 2, 200µg of 1 and 25µg of 2, 200µg of 1 and 50µg of 2, 200µg of 1 and 100µg of 2, 200µg of 1 and 150µg of 2, 200µg of 1

and 200ug of 2, 200|jg of 1 and 250|jg of 2, 250|jg of 1 and 25|jg of 2, 250[jg of 1 and 50ug of 2, 250ug of 1 and 1OOug of 2, 250ug of 1 and 150ug of 2, 250}jg of 1 and 200|jg of 2, 250)jg of 1 and 250ug of 2, 500ug of 1 and 25ug of 2, 500ug of 1 and 50|jg of 2, SOOug of 1 and 100|jg of 2, SOOpg of 1 and 150fjg of 2, SOOug of 1 and 200|jg of 2, SOOug of 1 and 250[jg of 2.

The active substance combinations of **1** and **2** as disclosed herein are preferably administered by inhalation. For this purpose, ingredients **1** and **2** have to be made available in forms suitable for inhalation. Inhalable preparations 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 can also include concentrates or sterile inhalable solutions ready for use. The preparations as disclosed may contain the combination of active substances **1** and **2** either together in one formulation or in two separate formulations. These formulations which may be used are described in more detail in the next part of the specification.

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

The inhalable powders as disclosed 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, trehalose), 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. Lactose is the particularly preferred excipient, while lactose monohydrate is most particularly preferred.

Within the scope of the inhalable powders disclosed herein, the excipients have 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 5µm, 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 and 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 36 325 685 A. Preferably, the Inhalable powders which contain physiologically acceptable excipients 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 in inhalettes is shown in Figure 1.

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 8 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 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, preferably 3 to 20mg, more particulary 5 to 10mg of Inhalable powder per capsule. These capsules can contain, either together or separately, the doses of 1 or 1' and 2 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 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 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 are known from the prior art. Suitable propellant gases are selected from among hydrocarbons such as 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, TG12, TG134a (1,1,1,2-tetrafluoroethane) and TG227 (1,1,1,2,3,3,3-heptafluoropropane) and mixtures thereof, of which the propellant gases TG134a, TG227 and mixtures thereof are preferred.

The propellant-driven inhalation aerosols may also contain other ingredients such as co-solvents, stabilisers, surfactants, antioxidants, lubricants, preservatives 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 can 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 10µm, preferably from 0.1 to 6µm , more preferably from 1 to 5µm.

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

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

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 the maximum is up to 70 percent by volume, more particularly up to 60 percent by volume and most preferably up to 30 percent by volume. The remainder of the volume is made up of water. The solutions or suspensions containing **1** and **2**, separately or together, can be 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 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 as disclosed. 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 physiologically 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 as disclosed herein are administered in particular using inhalers of the kind which are capable of nebulising a small amount of 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 100µL, preferably less than 50µL, more preferably between 20 and 30µL of active substance solution can be nebulised in preferably one spray action to form an aerosol with an average particle size of less than 20µm, preferably less than 10µm, 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 known by the name Respimat®.

This nebuliser (Respimat®) can be used to produce the inhalable aerosols as disclosed herein 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 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

- 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,
- 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.

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 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.

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

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

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 annual 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 advantageously be used for inhaling the aqueous aerosol preparations according to the invention.

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 as disclosed herein 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 may also be nebulised by means of inhalers other than those described above, e.g. jet stream inhalers.

Pharmaceutical formulations in the form of propellant-free inhalable solutions or suspensions as described above can combine with a device suitable for administering these formulations, preferably in conjunction with the Respimat®. Preferably, propellant-free inhalable solutions or suspensions can be characterised by the combination of active substances **1** and **2** in conjunction with the device known by the name Respimat®. In addition, the above-mentioned devices for inhalation, preferably the Respimat®, can be characterized in that they contain the

propellant-free inhalable solutions or suspensions as described hereinbefore.

The propellant-free inhalable solutions or suspensions 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.

Disclosed herein 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 used within the scope of the present invention which are not known in the art will be described.

Preparation of the compounds of formula 1:

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 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 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 Na_2SO_4, evaporated to dryness and the hydrochloride is precipitated from the residue. The product is purified by recrystallisation from acetonitrile.

Yield: 20.85 g (= 47 % of theory)

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

m.p.: 203-204°C.

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 dryness and the residue is recrystallised from isopropanol.

Yield: 11,34 g (= 75 % of theory); m.p.: 208-209°C.

$C_{24}H_{28}NO_3xBr$ (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.

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
1'-bromide	100
budesonide	200
lactose	4700
Total	5000

2)

Ingredients	µg per capsule
1'-bromide	100
Fluticasone-propionate	125
lactose	4775
Total	5000

3)

Ingredients	µg per capsule
1'-bromide	100
Mometasone-furoate X H_2O	250
lactose	4650
Total	5000

4)

Ingredients	µg per capsule
1'-bromide	100
Ciclesonide	250
lactose	4650
Total	5000

5)

Ingredients	µg per capsule
1'-bromide	50
budesonide	125
lactose	4825
Total	5000

6)

Ingredients	µg per capsule
1'-bromide	50
Fluticasone-propionate	200
lactose	4750
Total	5000

7)

Ingredients	µg per capsule
1'-bromide	75
Mometasone-furoate X H_2O	250
lactose	4675
Total	5000

8)

Ingredients	µg per capsule
1'-bromide	75
Ciclesonide	250
lactose	4675
Total	5000

9)

Ingredients	µg per capsule
1'-bromide	100
ST-126	250
lactose	4650
Total	5000

10)

Ingredients	µg per capsule
1'-bromide	50
ST-126	125
lactose	4825
Total	5000

B) Propellant-containing aerosols for inhalation:

1) Suspension aerosol:

Ingredients	% by weight
1'-bromide	0.020
budesonide	0.4
soya lecithin	0.2
TG 134a : TG227 = 2:3	ad 100

2) Suspension aerosol:

Ingredients	% by weight
1'-bromide	0.020
Fluticasone-propionate	0.3
Isopropyl myristate	0.1
TG 227	ad 100

3) Suspension aerosol:

Ingredients	% by weight
1'-bromide	0.020
Mometasone-furoate X H_2O	0.6
Isopropyl myristate	0.1
TG 227	ad 100

4) Suspension aerosol:

Ingredients	% by weight
1'-bromide	0.020
Ciclesonide	0.4
Isopropyl myristate	0.1
TG 134a : TG227 = 2:3	ad 100

5) Solution aerosol:

Ingredients	% by weight
1'-bromide	0.039
budesonide	0.4
absolute ethanol	0.5
Isopropyl myristate	0.1
TG 134a : TG227 = 2:3	ad 100

6) Solution aerosol:

Ingredients	% by weight
1'-bromide	0.039
Fluticasone-propionate	0.3
absolute ethanol	0.5
Isopropyl myristate	0.1
TG 134a : TG227 = 2:3	ad 100

7) Solution aerosol:

Ingredients	% by weight
1'-bromide	0.039
Mometasone-furoate X H_2O	0.6
absolute ethanol	0.5
Isopropyl myristate	0.1
TG 134a : TG227 = 2:3	ad 100

8) Solution aerosol:

Ingredients	% by weight
1'-bromide	0.039
Ciclesonide	0.4
absolute ethanol	0.5
Isopropyl myristate	0.1
TG 134a : TG227 = 2:3	ad 100

9) Solution aerosol:

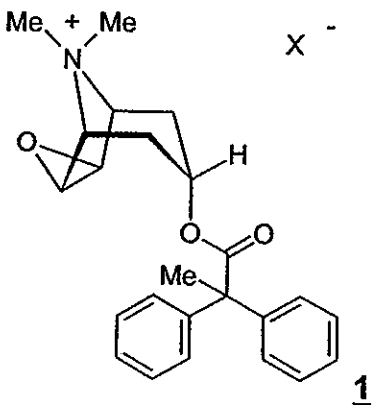
Ingredients	% by weight
1'-bromide	0.039
ST-126	0.6
absolute ethanol	0.5
Isopropyl myristate	0.1
TG 134a : TG227 = 2:3	ad 100

10) Solution aerosol:

Ingredients	% by weight
1'-bromide	0.039
ST-126	0.4
absolute ethanol	0.5
Isopropyl myristate	0.1
TG 134a : TG227 = 2:3	ad 100

Patent Claims

1) Pharmaceutical compositions, characterised in that they contain one or more, preferably one, salt of formula **1**



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,

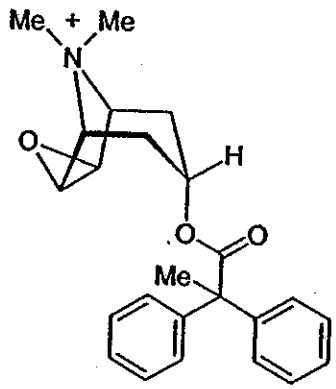
combined with one or more, preferably one, steroid **2**, optionally in the form of the diastereomers, mixtures of the diastereomers or in the form of the racemates thereof, optionally in the form of the solvates or hydrates and optionally together with a pharmaceutically acceptable excipient.

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.

3) Pharmaceutical composition according to claim 1 or 2, characterised in that the steroids **2** are flunisolide, beclomethasone, triamcinolone, budesonide, fluticasone, mometasone, ciclesonide, rofleponide, ST-126 or dexamethasone.

4) Pharmaceutical composition according to claim 3, characterised in that the steroids **2** are budesonide, fluticasone, mometasone, ciclesonide or ST-126 .

5) Pharmaceutical composition according to one of claims 1 to 4, characterised in that the weight ratios of **1'**



1'

to steroid **2** are in the range from 1:250 to 250:1, preferably in the range from 1:150 to 150:1.

6) Pharmaceutical composition according to one of claims 1 to 5, characterised in that it is in the form of a preparation suitable for inhalation.

7) Pharmaceutical composition according to claim 6, characterised in that it is a preparation selected from among the inhalable powders, propellant-containing metered-dose aerosols and propellant-free inhalable solutions or suspensions.

8) Pharmaceutical composition according to claim 7, 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.

9) Inhalable powder according to claim 8, characterised in that the excipient has a maximum average particle size of up to 250µm, preferably between 10 and 150µm.

10) Pharmaceutical composition according to claim 7, characterised in that it is an inhalable powder which contains only the active substances **1** and **2** as its ingredients.

11) Pharmaceutical composition according to claim 7, characterised in that it is a propellant-containing inhalable aerosol which contains 1 and 2 in dissolved or dispersed form.

12) Propellant-containing inhalable aerosol according to claim 11, 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.

13) Propellant-containing inhalable aerosol according to claim 12, characterised in that the propellant gas is TG11, TG12, TG134a, TG227 or mixtures thereof, preferably TG134a, TG227 or a mixture thereof.

14) Propellant-containing inhalable aerosol according to claim 11, 12 or 13, characterised in that it may contain up to 5 % by weight of active substance 1 and 2.

15) Pharmaceutical composition according to claim 7, characterised in that it is a propellant-free inhalable solution which contains water, ethanol or a mixture of water and ethanol as solvent.

16) Inhalable solution according to claim 15, characterised in that it optionally contains other co-solvents and/or excipients.

17) Inhalable solution according to claim 16, 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.

18) Inhalable solutions according to one of claims 16 or 17, characterised in that they contain as excipients surfactants, stabilisers, complexing agents, antioxidants and/or preservatives, flavourings and/or vitamins.

19) Inhalable solutions according to claim 18, characterised in that they contain as complexing agents editic acid or a salt of editic acid, preferably sodium edetate.

20) Use of a composition according to one of claims 1 to 19 for preparing a medicament for the treatment of inflammatory and/or obstructive respiratory complaints, particularly asthma or COPD.