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(54) Titre : MEDICAMENTS ADMINISTRES PAR INHALATION CONTENANT UN ANTICHOLINERGIQUE, DU
SALMETEROL ET UN STEROIDE DU GROUPE CICLESONIDE OU MOMETASONE FUROATE
(54) Title: INHALATION MEDICAMENT CONTAINING AN ANTICHOLINESTERASE DRUG, SALMETEROL AND A
STEROID SELECTED FROM THE CICLESONIDE OR MOMETASONE FUROATE GROUP

(57) **Abrégé/Abstract:**

The invention relates to novel medicament compositions based on an anticholinesterase drug, salmeterol xinafoate and on a corticosteroid, selected from the ciclesonide or mometasone furoate group. The invention also relates to a method for producing these compositions and to their use for treating respiratory disorders.



Abstract

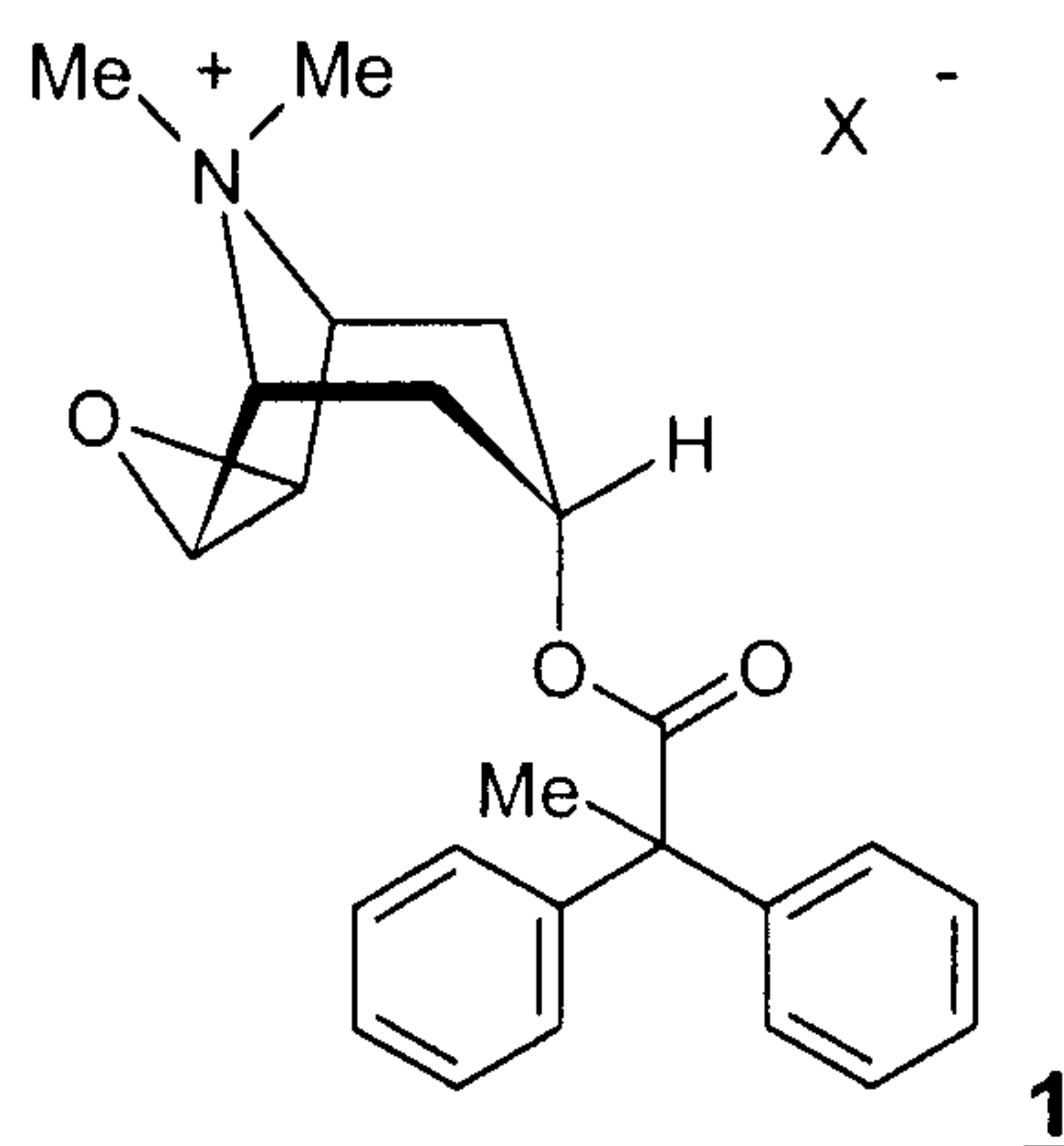
The present invention relates to novel pharmaceutical compositions based on a new anticholinergic, salmeterol salts and a corticosteroid, processes for preparing them
5 and their use in the treatment of respiratory complaints.

Inhalation medicament containing an anticholinesterase drug, salmeterol and a steroid selected from the ciclesonide or mometasone furoate group

- 5 The present invention relates to novel pharmaceutical compositions based on a new anticholinergic, salmeterol salts and a corticosteroid, processes for preparing them and their use in the treatment of respiratory complaints.

Description of the invention

- 10 The present invention relates to novel pharmaceutical compositions containing an anticholinergic of formula 1



wherein

- 15 X⁻ denotes an anion selected from among chloride, bromide and methanesulphonate, preferably bromide,

salmeterol xinafoate, optionally in the form of the hydrates and/or solvates thereof, and optionally in the form of one of the enantiomers or mixtures of enantiomers

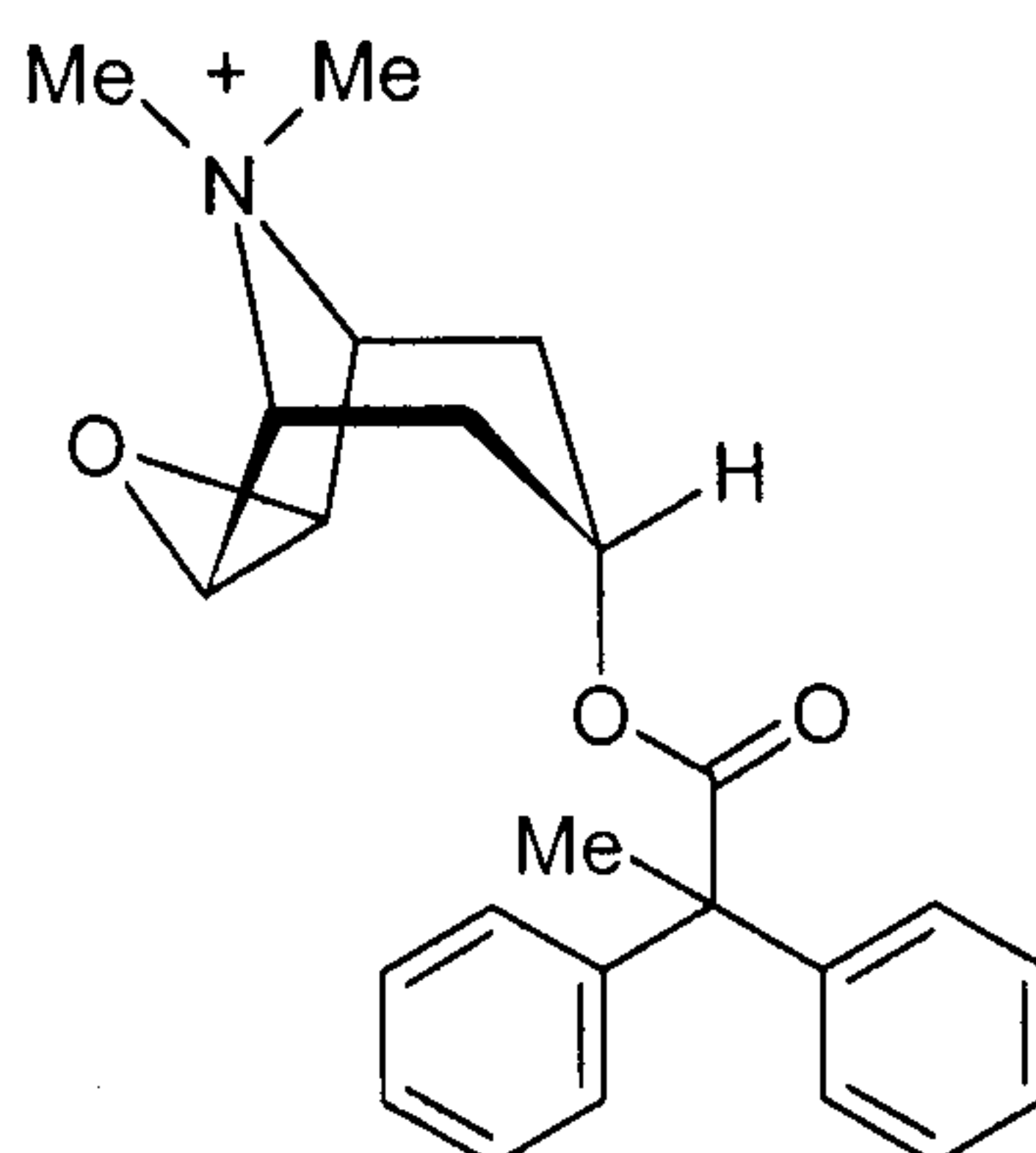
- 20 thereof,

and a steroid selected from among ciclesonide and mometasone furoate, optionally each in the form of the hydrates and/or solvates thereof.

- 25 The salts of formula 1 are known from International Patent Application WO 02/32899. Any reference to the salts of formula 1 includes a reference to any hydrates and solvates thereof which may be obtained.

- 30 Within the scope of the present patent application, an explicit reference to the pharmacologically active cation of formula

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can be recognised by the use of the designation 1'. Any reference to compounds 1 naturally includes a reference to the cation 1'.

5

Any reference to the steroids ciclesonide and mometasone furoate within the scope of the present invention includes a reference to 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 steroids mentioned may also occur in the form of their hydrates, and in the case of mometasone furoate, particular importance attaches to mometasone furoate monohydrate.

Salmeterol xinafoate may optionally be present in enantiomerically pure form. Enantiomers which may be used according to the invention are selected from among S-salmeterol xinafoate and R-salmeterol xinafoate, while R-salmeterol xinafoate is of particular importance. Salmeterol xinafoate may optionally be used in the form of the hydrate and/or solvate thereof. It is particularly preferred, especially when preparing powdered formulations, to use the salmeterol xinafoate which is characterised by a melting point of about 124°C.

The pharmaceutical combinations according to the invention are administered by inhalation according to the invention. Suitable inhalable powders packed into suitable capsules (inhalettes) may preferably be administered using suitable powder inhalers according to the invention. In one aspect, therefore, the present invention relates to a pharmaceutical composition which contains a combination of 1, salmeterol xinafoate and one of the steroids ciclesonide or mometasone furoate.

In another aspect the present invention relates to a pharmaceutical kit which contains the abovementioned ingredients in separate pharmaceutical formulations.

- 5 In another aspect the present invention relates to a medicament which contains, in addition to therapeutically effective amounts of 1, salmeterol xinafoate and ciclesonide or mometasone furoate, a pharmaceutically acceptable carrier. Particularly preferred medicaments contain, in addition to a pharmaceutically acceptable excipient or carrier, the following pharmaceutical combinations:
- 10 - 1'-bromide, salmeterol xinafoate and ciclesonide;
 - 1'-bromide, salmeterol xinafoate and mometasone furoate-monohydrate.

The present invention further relates to the use of the above-mentioned pharmaceutical combinations for preparing a pharmaceutical composition containing

15 therapeutically effective quantities of the three ingredients for treating inflammatory and/or obstructive diseases of the respiratory tract, particularly asthma and/or chronic obstructive pulmonary disease (COPD), by simultaneous or successive administration. In addition the pharmaceutical combinations according to the invention may be used to prepare a drug for treating cystic fibrosis or allergic

20 alveolitis (farmer's lung), for example, by simultaneous or successive administration. The combinations of active substances according to the invention will not be used only if treatment with one of the pharmaceutically active ingredients is contraindicated.

The present invention also relates to the simultaneous or successive use of

25 therapeutically effective doses of the combination of the above pharmaceutical compositions for treating inflammatory or obstructive diseases of the respiratory tract, particularly asthma and/or chronic obstructive pulmonary disease (COPD), provided that treatment with steroids or betamimetics is not contraindicated from a therapeutic point of view, by simultaneous or successive administration. The invention further

30 relates to the simultaneous or successive use of therapeutically effective doses of the combination of the above pharmaceutical compositions for treating cystic fibrosis or allergic alveolitis (farmer's lung), for example.

Preferred pharmaceutical combinations according to the invention which contain ciclesonide as steroid, are preferably administered according to the invention such that 15-800 µg, preferably 50-400 µg, particularly 50-200µg of active substance 1, preferably in the form of the bromide, 15 - 100 µg, preferably 30 to 75 µg salmeterol xinafoate and 50-400 µg, preferably 100 - 400 µg ciclesonide are given once or twice a day.

Preferred pharmaceutical combinations according to the invention which contain mometasone furoate as steroid are preferably administered according to the invention such that 15-800 µg, preferably 50-400 µg, particularly 50-200µg of active substance 1, preferably in the form of its bromide, 15 - 100 µg, preferably 30 to 75 µg salmeterol xinafoate and 200-800 µg, preferably 300 - 500 µg mometasone furoate, preferably in the form of its monohydrate, are administered once or twice a day.

The active substance combinations according to the invention are preferably administered by inhalation. For this purpose, ingredients have to be made available in forms suitable for inhalation.

Inhalable preparations include, according to the invention, inhalable powders, propellant-containing metered-dose aerosols or propellant-free inhalable solutions. Inhalable powders according to the invention containing the above-mentioned combinations of active substances may consist of the active substances on their own or of a mixture of the active substances with physiologically acceptable excipients. Within the scope of the present invention the term carrier may optionally be used instead of the term excipient. Within the scope of the present invention, the term propellant-free inhalable solutions also includes concentrates or sterile ready-to-use inhalable solutions. The preparations according to the invention may contain the combination of active substances either together in one, in two or in three separate formulations. These formulations which may be used within the scope of the present invention are described in more detail in the next part of the specification.

A) Inhalable powders:

The inhalable powders according to the invention may contain the above-mentioned active substances either on their own or in admixture with suitable physiologically acceptable excipients.

If the active substances are present in admixture with physiologically acceptable excipients, the following physiologically acceptable excipients may be used to prepare these inhalable powders according to the invention: monosaccharides (e.g. glucose or arabinose), disaccharides (e.g. lactose, saccharose, maltose, trehalose),
5 oligo- and polysaccharides (e.g. dextran), polyalcohols (e.g. sorbitol, mannitol, xylitol), salts (e.g. sodium chloride, calcium carbonate) or mixtures of these excipients. 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. For the purposes of the invention, lactose is the particularly preferred excipient, while
10 lactose monohydrate is most particularly preferred.

Within the scope of the inhalable powders according to the invention the excipients have a maximum average particle size of up to 250 μ m, preferably between 10 and 150 μ m, most preferably between 15 and 80 μ m. It may sometimes seem appropriate
15 to add finer excipient fractions with an average particle size of 1 to 9 μ m 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 according to the invention, the micronised active substances, preferably with an average particle size of 0.5 to 10 μ m, more preferably from 1 to 5 μ m, are added to
20 the excipient mixture. Processes for producing the inhalable powders according to the invention by grinding and micronising and by finally mixing the ingredients together are known from the prior art. The inhalable powders according to the invention may be prepared and administered either in the form of a single powder mixture which contains all three active substances or in the form of separate
25 inhalable powders which contain only two or only one of the above-mentioned active substances.

The inhalable powders according to the invention may be administered using inhalers known from the prior art.

Inhalable powders according to the invention which contain one or more
30 physiologically acceptable excipients in addition to the above-mentioned active substances 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. Preferably, the inhalable powders according to the invention which contain physiologically acceptable excipients in

addition to the above-mentioned active substances are packed into capsules (to produce so-called inhalettes) which are used in inhalers as described, for example, in WO 94/28958.

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

10 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 over 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, and air holes 13 for adjusting the flow resistance.

15 If the inhalable powders according to the invention are to be packed into capsules (inhalettes) for the preferred use described above, the quantities packed into each capsule should be 1 to 30 mg, preferably 3 to 20 mg, more particularly 5 to 10 mg of inhalable powder per capsule. These capsules contain, according to the invention, either together or separately, the doses of the above-mentioned active substances mentioned hereinbefore for each single dose.

20

B) Propellant-containing inhalation aerosols:

Inhalation aerosols containing propellant gas according to the invention may contain the above-mentioned active substances dissolved in the propellant gas or in dispersed form. The above-mentioned active substances may be present in separate formulations or in a single preparation, in which the above-mentioned active substances are either each dissolved, each dispersed or only one or two of the components are dissolved and the other is or are 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 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

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mixtures thereof. Particularly preferred propellant gases are halogenated alkane derivatives selected from TG134a and TG227 and mixtures thereof.

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

The propellant-driven inhalation aerosols according to the invention may contain up to 5 wt.-% of the above-mentioned active substances. 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 one or more of the above-
10 mentioned active substances.

If the active substances 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 5µm, more preferably from 1 to 5µm.

The propellant-driven inhalation aerosols according to the invention mentioned above
15 may be administered using inhalers known in the art (MDIs = metered dose inhalers). Accordingly, in another aspect, the present invention relates to 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, the present invention relates to inhalers which are characterised in that they
20 contain the propellant gas-containing aerosols described above according to the invention. The present invention also relates to cartridges which are fitted with a suitable valve and can be used in a suitable inhaler and which contain one of the above-mentioned propellant gas-containing inhalation aerosols according to the invention. Suitable cartridges and methods of filling these cartridges with the
25 inhalable aerosols containing propellant gas according to the invention are known from the prior art.

C) Propellant-free inhalable solutions or suspensions:

It is particularly preferred to use the active substance combination according to the invention in the form of propellant-free inhalable solutions and suspensions. The
30 solvent used may be an aqueous or alcoholic, preferably an ethanolic solution. The solvent may be water on its own or a mixture of water and ethanol. The relative

proportion of ethanol compared with water is not limited but the maximum is preferably 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 the above-mentioned active substances, 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. According to the invention, it is particularly preferred to use hydrochloric acid to adjust the pH.

According to the invention, the addition of editic acid (EDTA) or one of the known salts thereof, sodium edetate, 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 edetate is less than 100 mg/100 ml, preferably less than 50 mg/100 ml, more preferably less than 20 mg/100 ml. Generally, inhalable solutions in which the content of sodium edetate is from 0 to 10 mg/100 ml are preferred.

Co-solvents and/or other excipients may be added to the propellant-free inhalable solutions according to the invention. 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
5 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 physiologically acceptable salts such as sodium chloride as isotonic agents.

10 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
15 as sodium benzoate in the concentration known from the prior art. The preservatives mentioned above are preferably present in concentrations of up to 50 mg/100 ml, more preferably between 5 and 20 mg/100 ml.

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

The propellant-free inhalable solutions according to the invention are administered in particular using inhalers of the kind which are capable of nebulising a small amount of a liquid formulation in the required therapeutic dose within a few seconds to produce an aerosol suitable for therapeutic inhalation. Within the scope of the
25 present invention, preferred nebulisers 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
30 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 also known by the name
5 Respimat®.

This nebuliser (Respimat®) can advantageously be used to produce the inhalable aerosols according to the invention containing the combination of active substances according to the invention. 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 the pharmaceutical formulation at 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 plunger with
30 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 valve 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
25 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.

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.

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

10 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 6a/b of WO 97/12687, to which reference is explicitly made at this point, show the nebuliser (Respimat®) which can advantageously be used for inhaling the aqueous aerosol preparations according to the invention.

- 15 Figure 6a of WO 97/12687 shows a longitudinal section through the atomiser with the spring biased while Figure 6b of WO 97/12687 shows a longitudinal section through the atomiser with the spring relaxed.

- 20 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.
- 25 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.

- 30 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
5 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
10 according to the invention to produce an aerosol suitable for inhalation.

If the formulation according to the invention is nebulised using the technology 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).
15 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 according to the invention may also be nebulised by means of inhalers other than those described above, e.g. jet stream inhalers.

Accordingly, in a further aspect, the invention relates to pharmaceutical formulations
20 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, the invention relates to propellant-free inhalable solutions or suspensions characterised by the combination of active substances according to the invention in conjunction with the device known by the
25 name Respimat®. In addition, the present invention relates to the above-mentioned devices for inhalation, preferably the Respimat®, characterised in that they contain the propellant-free inhalable solutions or suspensions according to the invention as described hereinbefore.

The propellant-free inhalable solutions or suspensions according to the invention
30 may take the form of concentrates or sterile ready-to-use inhalable solutions or

suspensions, as well as the above-mentioned solutions and suspensions designed for use in a Respimat®. Ready-to-use formulations may be produced from the concentrates, for example, by the addition of isotonic saline solutions. Sterile ready-to-use formulations may be administered using energy-operated fixed or portable
5 nebulisers which produce inhalable aerosols by means of ultrasound or compressed air by the Venturi principle or other principles.

Accordingly, in another aspect, the present invention relates to pharmaceutical compositions in the form of propellant-free inhalable solutions or suspensions as described hereinbefore which take the form of concentrates or sterile ready-to-use
10 formulations, 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
15 without restricting the scope of the invention to the following embodiments by way of example.

Examples of formulations

A) Inhalable powders:

The Table that follows describes examples of inhalable powders according to the invention which contain 1'-bromide, salmeterol xinafoate, ciclesonide and lactose monohydrate as excipient.

Example	<u>1'</u> -salt [μg]	steroid [μg]	salmeterol xinafoate [μg]	excipient [μg]
1	50	400	50	4500
2	75	400	50	4475
3	100	400	50	4450
4	200	400	50	4350
5	400	400	50	4150
6	800	400	50	3750
7	50	300	50	4600
8	75	300	50	4575
9	100	300	50	4550
10	200	300	50	4450
11	400	300	50	4250
12	800	300	50	3850
13	50	200	50	4700
14	75	200	50	4675
15	100	200	50	4650
16	200	200	50	4550
17	400	200	50	4350
18	800	200	50	3950
19	50	400	35	4515
20	75	400	35	4490
21	100	400	35	4390
22	200	400	35	4365
23	400	400	35	4165
24	800	400	35	3765
25	50	300	35	4615
26	75	300	35	4590
27	100	300	35	4565
28	200	300	35	4465
29	400	300	35	4265
30	800	300	35	3865

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31	50	200	35	4715
32	75	200	35	4690
33	100	200	35	4665
34	200	200	35	4565
35	400	200	35	4365
36	800	200	35	3965
37	50	400	15	4535
38	75	400	15	4510
39	100	400	15	4485
40	200	400	15	4385
41	400	400	15	4185
42	800	400	15	3785
43	50	300	15	4635
44	75	300	15	4610
45	100	300	15	4585
46	200	300	15	4485
47	400	300	15	4285
48	800	300	15	3885
49	50	200	15	4735
50	75	200	15	4710
51	100	200	15	4685
52	200	200	15	4585
53	400	200	15	4385
54	800	200	15	3985
55	50	400	7.5	4542.5
56	75	400	7.5	4517.5
57	100	400	7.5	4492.5
58	200	400	7.5	4392.5
59	400	400	7.5	4192.5
60	800	400	7.5	3792.5
61	50	300	7.5	4642.5
62	75	300	7.5	4617.5
63	100	300	7.5	4592.5
64	200	300	7.5	4492.5
65	400	300	7.5	4292.5

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66	800	300	7.5	3892.5
67	50	200	7.5	4742.5
68	75	200	7.5	4717.5
69	100	200	7.5	4692.5
70	200	200	7.5	4592.5
71	400	200	7.5	4392.5
72	800	200	7.5	3992.5
73	50	400	75	4475
74	75	400	75	4450
75	100	400	75	4425
76	200	400	75	4325
77	400	400	75	4125
78	800	400	75	3725
79	50	300	75	4575
80	75	300	75	4550
81	100	300	75	4525
82	200	300	75	4425
83	400	300	75	4225
84	800	300	75	3825
85	50	200	75	4675
86	75	200	75	4650
87	100	200	75	4625
88	200	200	75	4525
89	400	200	75	4325
90	800	200	75	3925

The Table that follows describes examples of inhalable powders according to the invention which contain 1'-bromide, salmeterol xinafoate, mometasone furoate, and lactose monohydrate as excipient.

Example	<u>1'</u> -salt [μ g]	steroid [μ g]	salmeterol xinafoate [μ g]	excipient [μ g]
1	50	400	50	4500
2	75	400	50	4475
3	100	400	50	4450
4	200	400	50	4350
5	400	400	50	4150
6	800	400	50	3750
7	50	300	50	4600
8	75	300	50	4575
9	100	300	50	4550
10	200	300	50	4450
11	400	300	50	4250
12	800	300	50	3850
13	50	500	50	4400
14	75	500	50	4375
15	100	500	50	4350
16	200	500	50	4250
17	400	500	50	4050
18	800	500	50	3650
19	50	400	35	4515
20	75	400	35	4490
21	100	400	35	4390
22	200	400	35	4365
23	400	400	35	4165
24	800	400	35	3765
25	50	300	35	4615
26	75	300	35	4590
27	100	300	35	4565
28	200	300	35	4465
29	400	300	35	4265
30	800	300	35	3865

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31	50	500	35	4415
32	75	500	35	4390
33	100	500	35	4365
34	200	500	35	4265
35	400	500	35	4065
36	800	500	35	3665
37	50	400	15	4535
38	75	400	15	4510
39	100	400	15	4485
40	200	400	15	4385
41	400	400	15	4185
42	800	400	15	3785
43	50	300	15	4635
44	75	300	15	4610
45	100	300	15	4585
46	200	300	15	4485
47	400	300	15	4285
48	800	300	15	3885
49	50	500	15	4435
50	75	500	15	4410
51	100	500	15	4385
52	200	500	15	4285
53	400	500	15	4085
54	800	500	15	3685
55	50	400	7.5	4542.5
56	75	400	7.5	4517.5
57	100	400	7.5	4492.5
58	200	400	7.5	4392.5
59	400	400	7.5	4192.5
60	800	400	7.5	3792.5
61	50	300	7.5	4642.5
62	75	300	7.5	4617.5
63	100	300	7.5	4592.5
64	200	300	7.5	4492.5
65	400	300	7.5	4292.5

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66	800	300	7.5	3892.5
67	50	500	7.5	4442.5
68	75	500	7.5	4417.5
69	100	500	7.5	4392.5
70	200	500	7.5	4292.5
71	400	500	7.5	4092.5
72	800	500	7.5	3692.5
73	50	400	75	4475
74	75	400	75	4450
75	100	400	75	4425
76	200	400	75	4325
77	400	400	75	4125
78	800	400	75	3725
79	50	300	75	4575
80	75	300	75	4550
81	100	300	75	4525
82	200	300	75	4425
83	400	300	75	4225
84	800	300	75	3825
85	50	500	75	4375
86	75	500	75	4350
87	100	500	75	4325
88	200	500	75	4225
89	400	500	75	4025
90	800	500	75	3625

B) Propellant-containing inhalable aerosols:

The Table that follows describes examples of propellant-containing inhalable aerosols according to the invention which contain 1'-bromide, salmeterol xinafoate and ciclesonide. The amounts specified are percent by weight (based on the total formulation).

Extrac ted- ample	<u>1'</u> -salt	steroid	sal.- xinafoate	isopropyl- myristate	soya lecithin	ethanol (abs)	propell- ant gas [ad 100]
1	0.035	0.4	0.066	-	0.2	0.2	TG134a/ TG227 2:3
2	0.030	0.4	0.066	-	0.2	0.2	TG227
3	0.025	0.4	0.033	0.1	-	-	TG227
4	0.025	0.2	0.066	-	0.2	0.5	TG134a/ TG227 2:3
5	0.030	0.2	0.066	0.1	-	0.3	TG227
6	0.025	0.2	0.033	0.1	-	-	TG227
7	0.020	0.4	0.066	0.1	-	0.5	TG134a/ TG227 2:3
8	0.035	0.45	0.08	-	0.2	0.5	TG227
9	0.035	0.4	0.033	0.1	-	-	TG227
10	0.025	0.2	0.066	0.1	-	0.5	TG134a/ TG227 2:3

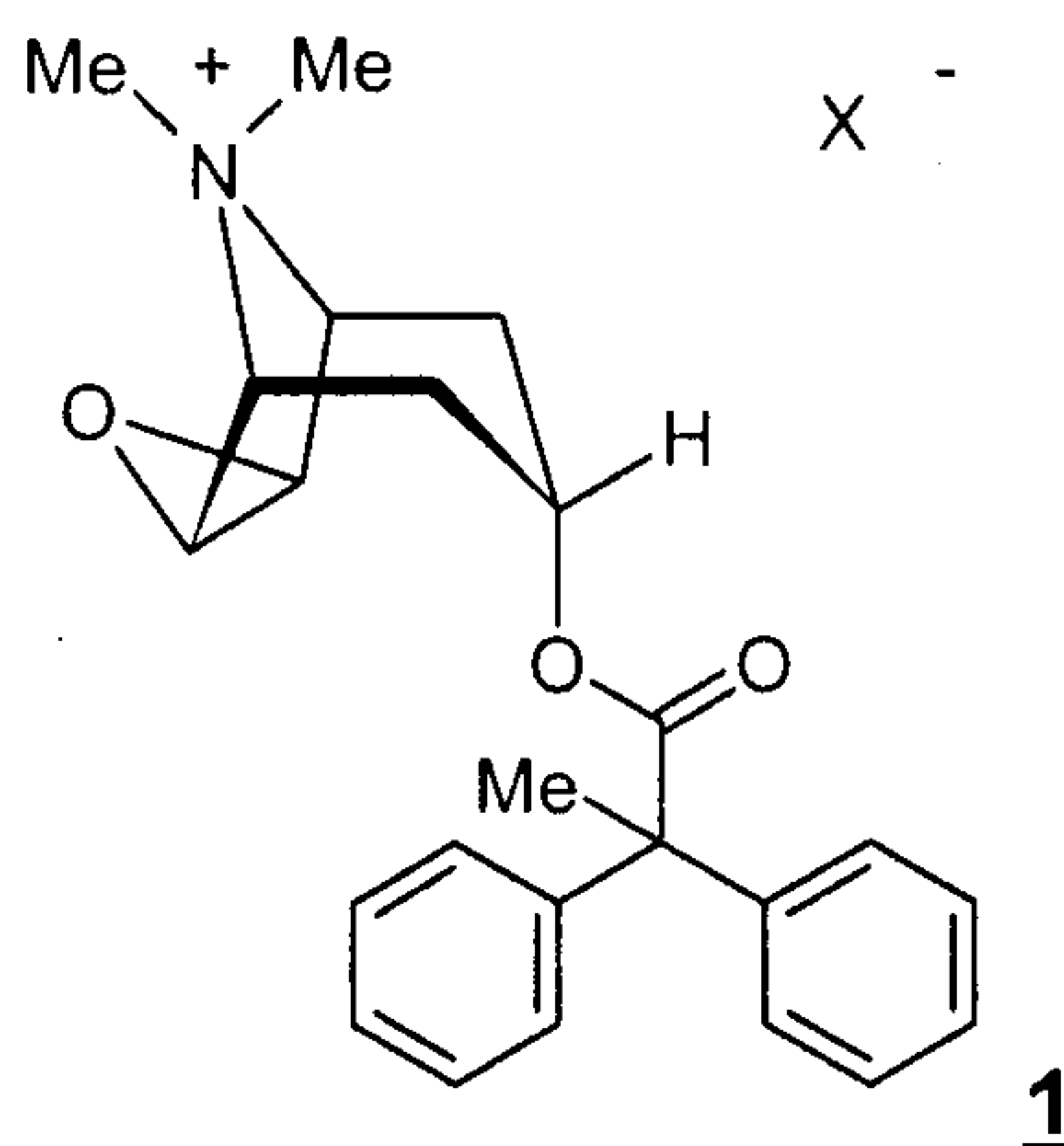
The Table that follows describes examples of propellant-containing inhalable aerosols according to the invention which contain 1'-bromide, salmeterol xinafoate and mometasone furoate. The amounts specified are percent by weight (based on the total formulation).

5

Ex-ample	<u>1'</u> -salt	steroid	sal.-xinafoate	isopropyl-myristate	soya lecithin	ethanol (abs)	propell-ant gas [ad 100]
1	0.035	0.4	0.066	-	0.2	0.2	TG134a/ TG227 2:3
2	0.030	0.4	0.066	-	0.2	0.2	TG227
3	0.025	0.4	0.033	0.1	-	-	TG227
4	0.035	0.2	0.066	-	0.2	0.2	TG134a/ TG227 2:3
5	0.030	0.2	0.066	0.1	-	0.5	TG227
6	0.025	0.2	0.033	0.1	-	-	TG227
7	0.039	0.4	0.066	0.1	-	0.5	TG134a/ TG227 2:3
8	0.039	0.45	0.08	-	0.2	0.5	TG227
9	0.039	0.4	0.033	0.1	-	-	TG227
10	0.035	0.2	0.066	0.1	-	0.5	TG134a/ TG227 2:3

Patent Claims

1) Pharmaceutical composition containing an anticholinergic of formula 1



5

wherein

X⁻ denotes an anion selected from among chloride, bromide and methanesulphonate, preferably bromide,

10 salmeterol xinafoate, optionally in the form of the hydrates and/or solvates thereof, and optionally in the form of one of the enantiomers or mixtures of enantiomers thereof,

15 and a steroid selected from among ciclesonide and mometasone furoate, optionally each in the form of the solvates and/or hydrates thereof, and optionally together with a physiologically acceptable excipient.

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

3) Pharmaceutical composition according to one of claims 1 or 2, characterised in that 1 is present in the form of the bromide thereof.

25 4) Pharmaceutical composition according to one of claims 1 to 3, characterised in that it is present in the form of a preparation suitable for inhalation.

5) Pharmaceutical composition according to claim 4, 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.

5 6) Pharmaceutical composition according to claim 5, characterised in that it is an inhalable powder which contains active substances 1, salmeterol xinafoate and steroid in admixture with suitable physiologically acceptable excipients selected from among the monosaccharides, disaccharides, oligo- and polysaccharides, polyalcohols, salts, or mixtures of these excipients.

10

7) Pharmaceutical composition according to claim 5, characterised in that it is a propellant-containing inhalable aerosol which contains the active substances 1, salmeterol xinafoate and steroid in dissolved or dispersed form and contains as propellant gas hydrocarbons such as n-propane, n-butane or isobutane or
15 halohydrocarbons such as chlorinated and/or fluorinated derivatives of methane, ethane, propane, butane, cyclopropane or cyclobutane.

8) Pharmaceutical composition according to claim 7, characterised in that the propellant gas is TG134a, TG227 or a mixture thereof.

20

9) Pharmaceutical composition according to claim 5, characterised in that it is a propellant-free inhalable solution or suspension containing water, ethanol or mixtures thereof as solvents.

25

10) Use of a composition according to one of claims 1 to 9 for preparing a medicament for the treatment of inflammatory and/or obstructive respiratory complaints.

30

11) Use of a composition according to claim 10 for preparing a medicament for the treatment of asthma or COPD.

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