Inhaler

The present invention relates to an inhaler according to the preamble of claim 1 and the use of an add-on device having a chamber for the intermediate storage of an atomised medicament preparation.

The present invention relates in particular to a so-called soft mist inhaler (SMI), i.e. an inhaler of the type which produces only a relatively slowly spreading spray mist (aerosol). Inhalers of this kind for the purposes of the present invention are in particular inhalers in which an aerosol is delivered at a speed of less than 2 m/s, preferably less than 1.5 m/s and most preferably less than 1 m/s (in each case measured at a distance of 10 cm from a dispensing nozzle).

The starting point of the present invention is an inhaler as described in principle in WO 91/14468 A1 and specifically in WO 97/12687 A1 (Figs. 6a, 6b). The known inhaler comprises as a reservoir for a medicament preparation which is to be atomised an insertible, rigid container having an inner bag containing the medicament preparation and a pressure producing means having a drive spring for conveying and nebulising the medicament preparation. Atomisation is carried out without the use of a propellant gas, namely by the force of the drive spring. This inhaler is an SMI in the sense of the present invention.

A problem with inhalers and SMIs in general is that the triggering of the atomisation of the medicament preparation and breathing in have to be coordinated. This may be difficult for the individual user. In particular, it has been found that such coordination is very difficult specifically for children. Studies have shown that the aerosol produced by unskilled users or, for example, children is often not optimally inhaled.

WO 2004/091704 A1 discloses an add-on device for the intermediate storage of an atomised medicament preparation in a chamber. The add-on device is used in a so-called metered dose inhaler (MDI). The MDI comprises a pressurised container

which contains the medicament preparation that is to be atomised and propellant gas. On actuation, the medicament preparation is expelled by means of the propellant gas at comparatively high pressure and correspondingly high speed and with a high mass flow. As a result, the expulsion is very brief, lasting in particular for less than 0.4 s, usually for about 0.15 to 0.36 s. The short expulsion time is disadvantageous for inhalation as the process of breathing in for inhalation usually lasts considerably longer. The comparatively high speed of more than 2 m/s often even above 8 m/s, at which the aerosol is usually delivered by an MDI, is also disadvantageous for receiving it into the lungs as the particles (droplets) of the aerosol are largely deposited on the walls of the user's throat as a result of the high speed during direct inhalation.

The known add-on device is provided for an MDI and serves to slow down the aerosol, particularly by lengthening the flow path. For this reason, add-on devices of this kind are also known as spacers. Moreover, the add-on device serves for intermediate storage of the aerosol produced so that the user has sufficient time to inhale the aerosol.

Object of the present invention is to provide an inhaler, most preferably an SMI, and the use of an add-on device with a chamber for intermediate storage of an atomised medicament preparation, thereby making it possible to simplify inhalation even of aerosols delivered at low speed and/or preventing or at least minimising problems occurring in the coordination of breathing in and the operation of an inhaler.

The above object is achieved by means of an inhaler according to claim 1 or its use according to claim 12. Advantageous embodiments are subject of the subclaims.

The present invention is based on the idea of combining a portable nebuliser for propellant-free nebulising of a medicament preparation or an SMI with an add-on device comprising a chamber for intermediate storage of the aerosol produced, the chamber being arranged downstream of a delivery nozzle of the inhaler.

It has been found that thanks to the add-on device, even in an inhaler which produces the aerosol that is to be inhaled over a comparatively long time, preferably more than 1 second, and/or at comparatively low speed, preferably less than 2 m/s, most preferably less than 1.5 m/s (measured at a distance of 10 cm from a delivery nozzle), it is possible to achieve surprisingly improved inhalation of the active substance, particularly in small children or other people who have problems of coordination. Coordinating the actuation of the inhaler, i.e. the production of the aerosol, and breathing in is made substantially easier. The aerosol is produced by the inhaler and sprays into the chamber of the add-on device. The user can then inhale the aerosol by breathing in as deeply as possible but without any compulsion of coordination or synchronisation.

The proposed solution allows better defined inhalation of the active substance with a content of active substance which is, in the last analysis, higher on average and/or fluctuates less, this active substance being deposited in the lungs. This allows improved therapy of children and/or a broadening of the indication or the use of other medicament preparations. Thus, in the last analysis, it renders a propellant free inhaler or SMI universally usable.

Preferably, the add-on device has a valve so as to prevent the user from breathing out into the inhaler or chamber, i.e. to prevent air from flowing back from the delivery side of the add-on device into the chamber.

Further advantages, features, properties and aspects of the present invention will become apparent from the claims and the following description of a preferred embodiment according to the drawings, wherein:

Fig. 1 is a schematic section through an inhaler in the untensioned state;

Fig. 2 is a schematic section through the inhaler, rotated through 90° relative to Fig. 1, in the tensioned state;

Fig. 3 is a schematic section through the inhaler, corresponding to Fig. 1, with the add-on device attached;

Fig. 4 is a schematic exploded view of the nebuliser and the add-on device with different accessories; and

Fig. 5 is a schematic view of test results.

In the figures, the same reference numerals have been used for identical or similar parts where corresponding or comparable properties and advantages are achieved, even if the relevant description has not been repeated.

Figs. 1 and 2 show a proposed portable inhaler 1 for the propellant free nebulisation of a medicament preparation 2 in a schematic view in the untensioned state (Fig. 1) and in the tensioned state (Fig. 2). Figs. 1 and 2 show the inhaler 1 with a container 3 holding the medicament preparation 2.

During the nebulisation of the medicament preparation 2, preferably a liquid, a respirable aerosol 14 (Fig. 1) is formed which can be breathed in or inhaled by a user or patient (not shown). Normally, inhalation takes place at least once a day, but particularly several times a day, preferably at specified intervals of time, more particularly depending on the complaint suffered by the patient.

The inhaler 1 comprises the preferably insertible and optionally exchangeable container 3 holding the medicament preparation 2. The container 3 thus forms a reservoir for the medicament preparation 2 which is to be nebulised. Preferably, the container 3 contains a sufficient quantity of medicament preparation 2 or active substance for several doses of the medicament preparation 2, i.e. to allow a number of nebulisations or applications. A typical container 3 as disclosed in WO 96/06011 A1 holds a volume of about 2 to 10 ml. With regard to the preferred construction of the container 3 reference is additionally made to WO 00/49988 A2.

The container 3 is preferably substantially cylindrical or cartridge-shaped and can be inserted into the inhaler 1 from below, after it has been opened, and optionally exchanged. It is preferably of rigid construction, the medicament preparation 2 being contained in particular in a collapsible bag 4 in the container 3.

The inhaler 1 also comprises a conveying device, particularly a pressure generator 5, for conveying and nebulising the medicament preparation 2, particularly in a predetermined and optionally adjustable dosage amount in each case.

The inhaler 1 or pressure generator 5 comprises in particular a holder 6 for the container 3 and associated drive spring 7 which is only partly shown, preferably having an associated locking element 8 which is manually operable to release it, a conveying element, preferably a conveying tube 9 in the form of a capillary, with an optional valve, particularly a non-return valve 10, a pressure chamber 11 and/or a delivery nozzle 12, particularly in the region of a mouthpiece 13.

The container 3 is fixed in the inhaler 1 by means of the holder 6, particularly by a clamping or latching action, such that the conveying tube 9 protrudes into the container 3. The holder 6 may be constructed such that the container 3 can be exchanged.

When the drive spring 7 is axially tensioned, the holder 6 with the container 3 and the conveying tube 9 is moved downwards in the figures and the medicament preparation 2 - or more precisely the next dose - is sucked out of the container 3 into the pressure chamber 11 of the pressure generator 5 through the non-return valve 10.

During the subsequent release of tension after actuation of the locking element 8, the medicament preparation 2 in the pressure chamber 11 is placed under pressure by moving the conveying tube 9 back up, with the non-return valve 10 now closed, by releasing the tension on the drive spring 7, so that this conveying tube 9 now acts as a pressure ram. This pressure expels the medicament preparation 2 through the delivery nozzle 12, where it is nebulised into the preferably respirable aerosol 14, as shown in Figs. 1 and 3.

The user or patient (not shown) can inhale the aerosol 14, while preferably supply air can be sucked into the mouthpiece 13 through at least one supply air opening 15.

During the nebulisation process the container 3 is moved back into its original position by the drive spring 7. The container 3 thus performs a lifting movement during the tensioning process and during the nebulisation process.

The inhaler 1 comprises in particular a first housing part (upper part) 16 and an inner part 17 which is rotatable relative thereto (Fig. 2) having an upper part 17a and a lower part 17b (Fig. 1), while a second housing part (lower part) 18, which is in particular manually operable or rotatable, is releasably attached, in particular pushed onto the inner part 17, preferably by means of a safety closure or retaining element 19. In particular, the safety closure or retaining element 19 is constructed such that accidental opening of the inhaler 1 or removal of the second housing part 18 is prevented. In particular, in order to release the second housing part 18, the retaining element 19 has to be pressed in against spring force. In order to insert and/or replace the container 3, the second housing part 18 can be detached from the inhaler 1. The second housing part 18 preferably forms a cap-like lower housing part and/or engages around or over a lower free end portion of the container 3.

The second housing part 18 can be rotated relative to the first housing part 16, whereby the inner part 17 is also rotated. In this way the drive spring 7 is tensioned in the axial direction by means of a gear (not shown in detail) acting on the holder 6. During tensioning the container 3 is moved axially downwards or with its end portion (further) into the second housing part 18 or towards the end face thereof, until the container 3 assumes an end position shown in Fig. 2. In this state the drive spring 7 or inhaler 1 is clamped and locked.

The inhaler 1 preferably has a device for forcibly ventilating the container 3.

When tensioning first takes place, the container 3 is preferably pierced in its base or opened. In particular, an axially acting spring 20 arranged in the housing part 18 comes to abut on the container base 21 and with a piercing element 22 pierces the

container 3 or an in particular gas tight seal provided in the base for ventilation purposes when contact is first made.

The device for forcible ventilation is thus formed in this case by the piercing element 22, which is held or formed by the spring 20. However, other design solutions are also possible.

It should be noted that during the piercing for ventilation purposes only the outer shell of the container 3 is opened. The bag 4 containing the medicament preparation 2 remains undamaged. As the medicament formulation 2 is removed from the bag 4 through the conveying tube 9 the flexible bag 4 collapses. For pressure equalisation, ambient air can flow into the container 3 through the ventilation or piercing opening.

In order to use the inhaler 1, first of all the container 3 has to be inserted. This is preferably done by removing or pulling out the second housing part 18. The container 3 is then axially inserted or pushed into the inner part 17. At the same time the container 3 is opened at the head end or attached. This is done by means of the conveying element, i.e. the conveying tube 9, which pierces a seal preferably provided at the head end of the container 3 and is then inserted through a septum at the head end of the container 3 into the interior of the bag 4. Thus the fluidic connection between the container 3, or more accurately between the bag 4 in the container 3, via the conveying tube 9 to the pressure generator 5 or pressure chamber 11 is produced.

Then the second housing part 18 is pushed on again. The inhaler 1 can now be tensioned for the first time. At this stage the container 3 is then pierced at its base by the piercing element 22, i.e. forcibly ventilated, as explained previously.

Before being used for the first time and after the container 3 has been inserted and fluidically connected, the inhaler 1 is preferably tensioned and actuated several times. This so-called priming displaces any air present in the medicament preparation 2 in

the conveying tube 9 and in the pressure generator 5 to the delivery nozzle 12. The inhaler 1 is then ready for inhalation.

The quantity of medicament preparation 2 delivered per spray or nebulisation process is preferably about 10 µl to 50 µl, more particularly about 10 µl to 20 µl, most preferably about 15 µl.

The drive spring 7 is preferably installed in a biased state in order to achieve a high spring pressure. In the proposed inhaler 1 the pressurisation and conveying of the medicament preparation 2 during the nebulisation process namely takes place preferably only by spring force, and more particularly only by the force of the drive spring 7.

The inhaler 1 is preferably constructed such that the medicament preparation 2 in the pressure generator 5 or in the pressure chamber 11 reaches a pressure of 5 MPa to 60 MPa, particularly about 10 MPa to 50 MPa during delivery. Particularly preferably, during the delivery or nebulisation of the medicament preparation 2, a pressure of about 5 MPa to 60 MPa, more particularly about 10 to 30 MPa, is reached at the delivery nozzle 12 or at the nozzle openings thereof. The medicament preparation 2 is then converted into the aerosol 14, the droplets of which have an aerodynamic diameter of up to 20 µm, preferably about 3 µm to 10 µm. The nebulising activity or nebulising effect is achieved or further assisted by preferably intercepting jets delivered by the delivery nozzle 12.

The inhaler 1 is preferably constructed such that the aerosol 14 is delivered at low speed, particularly at a speed of less than 2 m/s, most preferably about 1.6 m/s or less (in each case measured at a distance of 10 cm from the delivery nozzle 12). The inhaler 1 is thus preferably in the form of an SMI. The low delivery speed can be obtained or assisted by intercepting jets of the medicament preparation 2, which are delivered by the delivery nozzle 12 and/or by a suitable choice of spring force.

Particularly preferably, the construction of the inhaler 1 is such that the aerosol generation lasts for more than 0.7 s, more preferably at least about 1 s and in particular at least 1.5 s. The time taken to nebulise a dose or to actuate the inhaler 1 is thus more than 0.7 s, more preferably at least about 1 s, more particularly more than 1.5 s.

The inhaler 1 has an add-on device 23 with a chamber 24 for intermediate storage of the aerosol 14 produced by the inhaler 1, as is shown in a schematic section in Fig. 3.

The chamber 24 is arranged or adapted to be arranged downstream of the delivery nozzle 12. It serves to receive and intermediately store the aerosol 14 produced by the inhaler 1.

Preferably, the add-on device 23 or its chamber 24 is at least substantially cylindrical, elongate or conical in construction.

Preferably, the chamber 24 is of larger cross section than the mouthpiece 13 of the inhaler 1 and/or it widens out at least in parts towards the delivery end or free end of the add-on device 23. This ensures that the aerosol 14 strikes a wall of the chamber 24 over the smallest possible area. In this way it is possible to minimise the deposition or settling of the nebulised medicament preparation 2 on the wall of the chamber.

The chamber 24 preferably has a volume of more than 0.1 l, particularly more than 0.2 l, most preferably about 0.2 to 0.6 l. In particular, the add-on device 23 or the size of the chamber 24 is adapted to the inhaler 1 such that the aerosol 14 produced on actuation of the inhaler 1 can be at least substantially entirely received by the chamber 24 without the aerosol 14 or the nebulised medicament preparation 2 essentially being deposited or settling on the inner wall of the chamber.

The add-on device 23 in the embodiment shown preferably comprises a housing 25 which is in particular elongate and/or cylindrical in construction.

The add-on device 23 or its housing 25 is preferably at least substantially rigid in construction. However, the add-on device 23, the chamber 24 or the housing 25 may theoretically also be flexible, inflatable and/or telescopic in construction, in order to minimise the space taken up when not in use and/or for transportation purposes, in particular.

The add-on device 23 or the housing 25 preferably has a connecting member 26 for connecting to the inhaler 1, particularly the mouthpiece 13 thereof.

Preferably, the add-on device 23 or the connecting member 26 can be fitted onto the mouthpiece 13, particularly by a clamping effect, and/or can be released again from the inhaler 1 or mouthpiece 13. However, the add-on device 23 may if necessary be connected or connectable to the inhaler 1 in a fixed or non-removable manner.

In the embodiment shown, the mouthpiece 13 preferably has at least one supply air opening 15. Particularly preferably, at least one supply air opening 15 remains open when the add-on device 23 has been attached, particularly fitted on, as shown in Fig. 3. This may be achieved for example by corresponding conical design of the mouthpiece 13 and a complementary design of the connecting member 26, by a stop (not shown) and/or other design features.

Preferably, the add-on device 23 is not rotatable relative to the inhaler 1. This is achieved in the embodiment by designing the mouthpiece 13 of the inhaler 1 with a non-circular but preferably oval outer contour to which the connecting member 26 is matched accordingly. However, other design solutions are also possible.

The add-on device 23 or housing 25 preferably comprises a delivery member 27 for delivering the aerosol 14. The delivery member 27 is preferably arranged on the end of the chamber 24 or of the housing 25 which is opposite the connecting member 26.

Particularly preferably, the connecting member 26 and the delivery member 27 are formed in one piece with the housing 25. However, other design solutions are also possible.

Preferably, the chamber 24 or the housing 25 is at least partly or totally transparent in construction. This assists cleaning, in particular.

The add-on device 23 preferably has, at the delivery end, a valve 28 for preventing air from flowing back into the chamber 24. In this way it is possible to prevent air from flowing into the chamber 24 as the user breathes out, which would force out the aerosol 14 through the attached mouthpiece 13 and the supply air openings 15, for example.

The valve 28 is preferably a non-return valve.

Particularly preferably, the valve 28 is incorporated in the connecting member 27. Particularly preferably, the valve 28 can be detached from the add-on device 23 or the housing 25, for example for cleaning purposes.

Alternatively or in addition to the valve 28 the proposed inhaler 1 may also have a valve device (not shown) in the region of the mouthpiece 13 and/or the supply air opening or openings 15 to prevent air from flowing back out of the chamber 24 through the mouthpiece 13 and out through the supply air opening or openings 15.

Alternatively or in addition, the add-on device 23 may also have an additional valve device (not shown), for example between the connecting member 26 and the mouthpiece 13, to allow air to flow into the chamber 24 but prevent it from flowing out. In this case the supply air openings 15 may be dispensed with altogether and/or may be covered or closed off by the add-on device 24.

Preferably, the add-on device 23 comprises, alternatively or in addition, at least one valve 32 for blowing out the exhaled air, as schematically shown in Fig. 3. In

particular, Fig. 3 shows two such valves 32 in the opened state. Valve flaps are lifted away from the associated outlet openings. The at least one valve 32 is preferably at the delivery end and in particular is arranged on the delivery member 27. However, other design solutions are also possible.

When a user (not shown) breathes in, the valve 28 opens, as shown by broken lines in Fig. 3. The valves 32 are closed. The aerosol 14 is sucked out of the chamber 24 and emitted through the delivery member 27. As the user breathes out, the valve 28 closes or is closed. The valves 32 open and allows the exhaled air to be blown out without this air flowing into the chamber 24 or affecting the aerosol 14.

The add-on device 23 or its delivery member 27 may be equipped at the delivery end, preferably with an add-on mouthpiece 29, a tube 30 and/or a face mask 31, as shown by way of example in Fig. 4. In particular, different end pieces such as the add-on mouthpiece 29, the tube 30 and/or the face mask 31 can be selectively attached to the add-on device 23 or its delivery member 27, most preferably by fitting on.

Tests have shown that the proposed use of the add-on device 23 with the inhaler 1, i.e. the proposed intermediate storage of the aerosol 14 produced by the inhaler 1 in a sufficiently large chamber 24 may substantially contribute to a higher proportion of the active substance being received in the lungs on inhalation, even where there are problems of co-ordination.

The enclosed Fig. 5 illustrates the proportion of active substance which is supplied for the lungs as a whole (DeT) and the proportion of active substance deposited in the throat (Throat) as a function of the overall dosage amount for different inhalers.

The vertical axis shows the percentage amount of the respective dose which is actually delivered, while DeT shows the proportion which is made available to the lungs on inhalation, and Throat indicates the proportion which is deposited in the throat. The deposition of active substance was determined on the basis of the

declared content using a Finlay throat model. An inhaled volume of 0.5 l in all was taken as the basis.

The tests were carried out for different apparatus or combinations of apparatus and at different flow rates, as plotted on the horizontal axis. RMT indicates the results of the inhaler 1 without the add-on device 23. RMT+AC indicates the results when the inhaler 1 is combined with the add-on device 23. pMDI+AC gives the results when a conventional MDI is combined with the add-on device 23. The numbers 5, 10, 20 and 30 each indicate the flow rate in l/min.

Fig. 5 shows that the use of the add-on device 23 leads to a reduction in the throat deposits. This is favourable for paediatric applications as active substance deposited in the throat generally does not contribute to the therapy but instead often leads to (systemic) side effects. The use of the add-on device 23 is good as a slight deposit in the throat can only be detected above a flow rate of 20 l/min when the add-on device 23 is used. At all the flow rates, the deposition in the throat with the proposed combination of the inhaler 1 (SMI) with the add-on device 23 is lower than that of the inhaler 1 (SMI) on its own. The DeT can be correlated with the possible therapeutic effect. The proposed combination of the inhaler 1 (SMI) with the add-on device 23 always has a higher DeT than a conventional MDI with the add-on device 23. The loss of DeT by the use of the add-on device 23 compared with the proposed inhaler 1 without the add-on device 23 is detectable but must be estimated as being substantially lower than in a conventional MDI. Therefore, with the proposed solution, a higher efficacy or a higher proportion of active substance reaching the lungs can be assumed.

To complete the disclosure of the present application and with regard to the preferred embodiment of the inhaler 1, reference is hereby made, by way of a precaution, to the total disclosure of both WO 91/14468 A1 and also WO 97/12687 A1.

In contrast to freestanding appliances or the like, the proposed inhaler 1 is preferably designed to be portable and in particular is a mobile hand-held device.

By virtue of its cylindrical shape and handy size of less than 9 to 15 cm long and 2 to 4 cm wide, the inhaler 1 can be carried by the patient at all times. The nebuliser sprays a defined volume of the medicament preparation 2 by the application of high pressure through small nozzles, so as to form inhalable aerosols 14.

The proposed inhaler 1 operates purely mechanically, in particular. However, the inhaler 1 may theoretically operate by any other method. In particular, the expression "conveying device" or "pressure generator" must be understood in very general terms. For example, the pressure required for the delivery and nebulisation may also be produced by propellant gas, a pump or any other suitable method.

The proposed inhaler 1 is designed in particular for the brief nebulisation of the medicament preparation 2, for example for one to two breaths. However, it may also be designed or used for longer or continuous nebulisation.

Some preferred ingredients, compounds and/or formulations of the medicament preparation 2 are listed below.

The compounds listed below may be used in the device according to the invention on their own or in combination. In the compounds mentioned below, **W** is a pharmacologically active substance and is selected (for example) from among the betamimetics, anticholinergics, corticosteroids, PDE4-inhibitors, LTD4-antagonists, EGFR-inhibitors, dopamine agonists, H1-antihistamines, PAF-antagonists and PI3-kinase inhibitors. Moreover, double or triple combinations of **W** may be combined and used in the device according to the invention. Combinations of **W** might be, for example:

- **W** denotes a betamimetic, combined with an anticholinergic, corticosteroid, PDE4-inhibitor, EGFR-inhibitor or LTD4-antagonist,
- **W** denotes an anticholinergic, combined with a betamimetic, corticosteroid, PDE4-inhibitor, EGFR-inhibitor or LTD4-antagonist,

- **W** denotes a corticosteroid, combined with a PDE4-inhibitor, EGFR-inhibitor or LTD4-antagonist
- **W** denotes a PDE4-inhibitor, combined with an EGFR-inhibitor or LTD4-antagonist
- **W** denotes an EGFR-inhibitor, combined with an LTD4-antagonist.

The compounds used as betamimetics are preferably compounds selected from among albuterol, arformoterol, bambuterol, bitolterol, broxaterol, carbuterol, clenbuterol, fenoterol, formoterol, hexoprenaline, ibuterol, isoetharine, isoprenaline, levosalbutamol, mabuterol, meluadrine, metaproterenol, orciprenaline, pirbuterol, procaterol, reproterol, rimiterol, ritodrine, salmefamol, salmeterol, soterenol, sulphonterol, terbutaline, tiaramide, tolubuterol, zinterol, CHF-1035, HOKU-81, KUL-1248 and

- 3-(4-{6-[2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-hexyloxy}-butyl)-benzyl-sulphonamide
- 5-[2-(5,6-diethyl-indan-2-ylamino)-1-hydroxy-ethyl]-8-hydroxy-1H-quinolin-2-one
- 4-hydroxy-7-[2-{[2-{[3-(2-phenylethoxy)propyl]sulphonyl}ethyl]-amino}ethyl]-2(3H)-benzothiazolone
- 1-(2-fluoro-4-hydroxyphenyl)-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol
- 1-[3-(4-methoxybenzyl-amino)-4-hydroxyphenyl]-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol
- 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-N,N-dimethylaminophenyl)-2-methyl-2-propylamino]ethanol
- 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-methoxyphenyl)-2-methyl-2-propylamino]ethanol
- 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-n-butyloxyphenyl)-2-methyl-2-propylamino]ethanol
- 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-{4-[3-(4-methoxyphenyl)-1,2,4-triazol-3-yl]-2-methyl-2-butylamino}ethanol
- 5-hydroxy-8-(1-hydroxy-2-isopropylaminobutyl)-2H-1,4-benzoxazin-3-(4H)-one

- 1-(4-amino-3-chloro-5-trifluoromethylphenyl)-2-tert.-butylamino)ethanol
- 6-hydroxy-8-{1-hydroxy-2-[2-(4-methoxy-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one
- 6-hydroxy-8-{1-hydroxy-2-[2-(ethyl 4-phenoxy-acetate)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one
- 6-hydroxy-8-{1-hydroxy-2-[2-(4-phenoxy-acetic acid)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one
- 8-{2-[1,1-dimethyl-2-(2,4,6-trimethylphenyl)-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one
- 6-hydroxy-8-{1-hydroxy-2-[2-(4-hydroxy-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one
- 6-hydroxy-8-{1-hydroxy-2-[2-(4-isopropyl-phenyl)-1.1dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one
- 8-{2-[2-(4-ethyl-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one
- 8-{2-[2-(4-ethoxy-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one
- 4-(4-{2-[2-hydroxy-2-(6-hydroxy-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl)-ethylamino]-2-methyl-propyl}-phenoxy)-butyric acid
- 8-{2-[2-(3.4-difluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one
- 1-(4-ethoxy-carbonylamino-3-cyano-5-fluorophenyl)-2-(tert-butylamino)ethanol
- 2-hydroxy-5-(1-hydroxy-2-{2-[4-(2-hydroxy-2-phenyl-ethylamino)-phenyl]-ethylamino}-ethyl)-benzaldehyde
- N-[2-hydroxy-5-(1-hydroxy-2-{2-[4-(2-hydroxy-2-phenyl-ethylamino)-phenyl]-ethylamino}-ethyl)-phenyl]-formamide
- 8-hydroxy-5-(1-hydroxy-2-{2-[4-(6-methoxy-biphenyl-3-ylamino)-phenyl]-ethylamino}-ethyl)-1H-quinolin-2-one
- 8-hydroxy-5-[1-hydroxy-2-(6-phenethylamino-hexylamino)-ethyl]-1H-quinolin-2-one
- 5-[2-(2-{4-[4-(2-amino-2-methyl-propoxy)-phenylamino]-phenyl}-ethylamino)-1-hydroxy-ethyl]-8-hydroxy-1H-quinolin-2-one

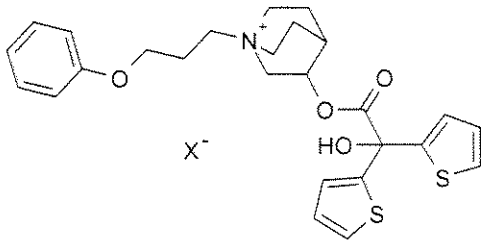
- [3-(4-{6-[2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-hexyloxy}-butyl)-5-methyl-phenyl]-urea
- 4-(2-{6-[2-(2,6-dichloro-benzyloxy)-ethoxy]-hexylamino}-1-hydroxy-ethyl)-2-hydroxymethyl-phenol
- 3-(4-{6-[2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-hexyloxy}-butyl)-benzylsulphonamide
- 3-(3-{7-[2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-heptyloxy}-propyl)-benzylsulphonamide
- 4-(2-{6-[4-(3-cyclopentanesulphonyl-phenyl)-butoxy]-hexylamino}-1-hydroxy-ethyl)-2-hydroxymethyl-phenol
- N-Adamantan-2-yl-2-(3-{2-[2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-propyl}-phenyl)-acetamide

optionally in the form of the racemates, enantiomers, diastereomers thereof and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof. According to the invention the acid addition salts of the betamimetics are preferably selected from among the hydrochloride, hydrobromide, hydriodide, hydrosulphate, hydrophosphate, hydromethanesulphonate, hydronitrate, hydromaleate, hydroacetate, hydrocitrate, hydrofumarate, hydrotartrate, hydroxalate, hydrosuccinate, hydrobenzoate and hydro-p-toluenesulphonate.

The anticholinergics used are preferably compounds selected from among the tiotropium salts, preferably the bromide salt, oxitropium salts, preferably the bromide salt, flutropium salts, preferably the bromide salt, ipratropium salts, preferably the bromide salt, glycopyrronium salts, preferably the bromide salt, trospium salts, preferably the chloride salt, tolterodine. In the above-mentioned salts the cations are the pharmacologically active constituents. As anions the above-mentioned salts may preferably contain the chloride, bromide, iodide, sulphate, phosphate, methanesulphonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate or p-toluenesulphonate, while chloride, bromide, iodide, sulphate, methanesulphonate or p-toluenesulphonate are preferred as counter-ions.

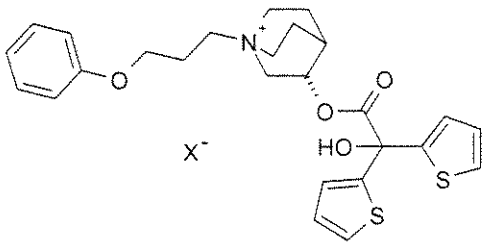
Of all the salts the chlorides, bromides, iodides and methanesulphonates are particularly preferred.

Other preferred anticholinergics are selected from among the salts of formula **AC-1**



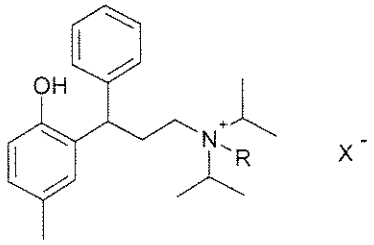
AC-1

wherein X $^-$ denotes an anion with a single negative charge, preferably an anion selected from among the fluoride, chloride, bromide, iodide, sulphate, phosphate, methanesulphonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate and p-toluenesulphonate, preferably an anion with a single negative charge, particularly preferably an anion selected from among the fluoride, chloride, bromide, methanesulphonate and p-toluenesulphonate, particularly preferably bromide, optionally in the form of the racemates, enantiomers or hydrates thereof. Of particular importance are those pharmaceutical combinations which contain the enantiomers of formula **AC-1-en**



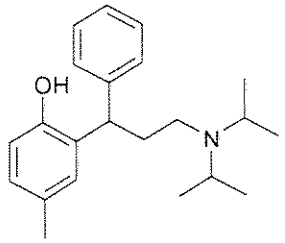
AC-1-en

wherein X $^-$ may have the above-mentioned meanings. Other preferred anticholinergics are selected from the salts of formula **AC-2**



AC-2

wherein R denotes either methyl or ethyl and wherein X $^-$ may have the above-mentioned meanings. In an alternative embodiment the compound of formula **AC-2** may also be present in the form of the free base **AC-2-base**.



AC-2-base

Other specified compounds are:

- tropenol 2,2-diphenylpropionate methobromide,
- scopine 2,2-diphenylpropionate methobromide,
- scopine 2-fluoro-2,2-diphenylacetate methobromide,
- tropenol 2-fluoro-2,2-diphenylacetate methobromide;
- tropenol 3,3',4,4'-tetrafluorobenzilate methobromide,
- scopine 3,3',4,4'-tetrafluorobenzilate methobromide,
- tropenol 4,4'-difluorobenzilate methobromide,
- scopine 4,4'-difluorobenzilate methobromide,
- tropenol 3,3'-difluorobenzilate methobromide,
- scopine 3,3'- difluorobenzilate methobromide;
- tropenol 9-hydroxy-fluorene-9-carboxylate methobromide;
- tropenol 9-fluoro-fluorene-9-carboxylate methobromide;
- scopine 9-hydroxy-fluorene-9-carboxylate methobromide;
- scopine 9-fluoro-fluorene-9-carboxylate methobromide;

- tropenol 9-methyl-fluorene-9-carboxylate methobromide;
- scopine 9-methyl-fluorene-9-carboxylate methobromide;
- cyclopropyltropine benzilate methobromide;
- cyclopropyltropine 2,2-diphenylpropionate methobromide;
- cyclopropyltropine 9-hydroxy-xanthene-9-carboxylate methobromide;
- cyclopropyltropine 9-methyl-fluorene-9-carboxylate methobromide;
- cyclopropyltropine 9-methyl-xanthene-9-carboxylate methobromide;
- cyclopropyltropine 9-hydroxy-fluorene-9-carboxylate methobromide;
- cyclopropyltropine methyl 4,4'-difluorobenzilate methobromide.
- tropenol 9-hydroxy-xanthene-9-carboxylate methobromide;
- scopine 9-hydroxy-xanthene-9-carboxylate methobromide;
- tropenol 9-methyl-xanthene-9-carboxylate methobromide;
- scopine 9-methyl-xanthene-9-carboxylate methobromide;
- tropenol 9-ethyl-xanthene-9-carboxylate methobromide;
- tropenol 9-difluoromethyl-xanthene-9-carboxylate methobromide;
- scopine 9-hydroxymethyl-xanthene-9-carboxylate methobromide,

The above-mentioned compounds may also be used as salts within the scope of the present invention, wherein instead of the methobromide the metho-X salts are used, wherein X may have the meanings given hereinbefore for X^-.

As corticosteroids it is preferable to use compounds selected from among beclomethasone, betamethasone, budesonide, butixocort, ciclesonide, deflazacort, dexamethasone, etiprednol, flunisolide, fluticasone, loteprednol, mometasone, prednisolone, prednisone, rofleponide, triamcinolone, RPR-106541, NS-126, ST-26 and

- (S)-fluoromethyl 6,9-difluoro-17-[(2-furanylcarbonyl)oxy]-11-hydroxy-16-methyl-3-oxo-androsta-1,4-diene-17-carbothionate
- (S)-(2-oxo-tetrahydro-furan-3S-yl)6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-propionyloxy-androsta-1,4-diene-17-carbothionate,
- cyanomethyl 6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-(2,2,3,3-tertamethylcyclopropylcarbonyl)oxy-androsta-1,4-diene-17β-carboxylate

optionally in the form of the racemates, enantiomers or diastereomers thereof and optionally in the form of the salts and derivatives thereof, the solvates and/or hydrates thereof. Any reference to steroids includes a reference to any salts or derivatives, hydrates or solvates thereof which may exist. Examples of possible salts and derivatives of the steroids may be: alkali metal salts, such as for example sodium or potassium salts, sulphobenzoates, phosphates, isonicotinates, acetates, dichloroacetates, propionates, dihydrogen phosphates, palmitates, pivalates or furoates.

PDE4-inhibitors which may be used are preferably compounds selected from among enprofyllin, theophyllin, roflumilast, ariflo (cilomilast), tofimilast, pumafentrin, lirimilast, arofyllin, atizoram, D-4418, Bay-198004, BY343, CP-325.366, D-4396 (Sch-351591), AWD-12-281 (GW-842470), NCS-613, CDP-840, D-4418, PD-168787, T-440, T-2585, V-11294A, Cl-1018, CDC-801, CDC-3052, D-22888, YM-58997, Z-15370 and

- N-(3,5-dichloro-1-oxo-pyridin-4-yl)-4-difluoromethoxy-3-cyclopropylmethoxybenzamide
- (-)p-[(4*a*R*,10*b*S*)-9-ethoxy-1,2,3,4,4a,10b-hexahydro-8-methoxy-2-methylbenzo[s][1,6]naphthyridin-6-yl]-N,N-diisopropylbenzamide
- (R)-(+)-1-(4-bromobenzyl)-4-[(3-cyclopentyloxy)-4-methoxyphenyl]-2-pyrrolidone
- 3-(cyclopentyloxy-4-methoxyphenyl)-1-(4-N'-[N-2-cyano-S-methyl-isothioureido]benzyl)-2-pyrrolidone
- cis[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid]
- 2-carbomethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)cyclohexan-1-one
- cis[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol]
- (R)-(+)-ethyl[4-(3-cyclopentyloxy-4-methoxyphenyl)pyrrolidin-2-ylidene]acetate
- (S)-(-)-ethyl[4-(3-cyclopentyloxy-4-methoxyphenyl)pyrrolidin-2-ylidene]acetate

- 9-cyclopentyl-5,6-dihydro-7-ethyl-3-(2-thienyl)-9*H*-pyrazolo[3,4-c]-1,2,4-triazolo[4,3-a]pyridine
- 9-cyclopentyl-5,6-dihydro-7-ethyl-3-(*tert*-butyl)-9*H*-pyrazolo[3,4-c]-1,2,4-triazolo[4,3-a]pyridine

optionally in the form of the racemates, enantiomers or diastereomers thereof and optionally in the form of the pharmacologically acceptable acid addition salts thereof, the solvates and/or hydrates thereof. According to the invention the acid addition salts of the betamimetics are preferably selected from among the hydrochloride, hydrobromide, hydriodide, hydrosulphate, hydrophosphate, hydromethanesulphonate, hydronitrate, hydromaleate, hydroacetate, hydrocitrate, hydrofumarate, hydrotartrate, hydroxalate, hydrosuccinate, hydrobenzoate and hydro-p-toluenesulphonate.

The LTD4-antagonists used are preferably compounds selected from among montelukast, pranlukast, zafirlukast, MCC-847 (ZD-3523), MN-001, MEN-91507 (LM-1507), VUF-5078, VUF-K-8707, L-733321 and

- 1-(((R)-(3-(2-(6,7-difluoro-2-quinolinyl)ethenyl)phenyl)-3-(2-(2-hydroxy-2-propyl)phenyl)thio)methylcyclopropane-acetic acid,
- 1-(((1(R)-3(3-(2-(2,3-dichlorothieno[3,2-b]pyridin-5-yl)-(E)-ethenyl)phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)propyl)thio)methyl)cyclopropaneacetic acid
- [2-[[2-(4-tert-butyl-2-thiazolyl)-5-benzofuranyl]oxymethyl]phenyl]acetic acid

optionally in the form of the racemates, enantiomers or diastereomers thereof and optionally in the form of the pharmacologically acceptable acid addition salts, solvates and/or hydrates thereof. According to the invention the acid addition salts of the betamimetics are preferably selected from among the hydrochloride, hydrobromide, hydriodide, hydrosulphate, hydrophosphate, hydromethanesulphonate, hydronitrate, hydromaleate, hydroacetate, hydrocitrate, hydrofumarate, hydrotartrate, hydroxalate, hydrosuccinate, hydrobenzoate and hydro-p-toluenesulphonate. By salts or derivatives which the LTD4-antagonists may optionally be capable of forming are meant, for example: alkali metal salts, such as for example sodium or potassium salts, alkaline earth metal salts, sulphobenzoates, phosphates, isonicotinates, acetates, propionates, dihydrogen phosphates, palmitates, pivalates or furoates.

EGFR-inhibitors which may be used are preferably compounds selected from among cetuximab, trastuzumab, ABX-EGF, Mab ICR-62 and

- 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]-amino}-7-cyclopropylmethoxy-quinazoline
- 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline
- 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline
- 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]-amino}-7-cyclopentyloxy-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((R)-2-methoxymethyl-6-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-((S)-6-methyl-2-oxo-morpholin-4-yl)-ethoxy]-7-methoxy-quinazoline
- 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline
- 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline
- 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-(N,N-to-(2-methoxy-ethyl)-amino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline
- 4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-ethyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline
- 4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline
- 4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(tetrahydropyran-4-yl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline
- 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((R)-tetrahydrofuran-3-yloxy)-quinazoline

- 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline
- 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopentyloxy-quinazoline
- 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N-cyclopropyl-N-methyl-amino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline
- 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(R)-(tetrahydrofuran-2-yl)methoxy]-quinazoline
- 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline
- 4-[(3-ethynyl-phenyl)amino]-6.7-to-(2-methoxy-ethoxy)-quinazoline
- 4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(morpholin-4-yl)-propyloxy]-6-[(vinyl-carbonyl)amino]-quinazoline
- 4-[(R)-(1-phenyl-ethyl)amino]-6-(4-hydroxy-phenyl)-7H-pyrrolo[2,3-d]pyrimidine
- 3-cyano-4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-ethoxy-quinoline
- 4-{[3-chloro-4-(3-fluoro-benzyloxy)-phenyl]amino}-6-(5-{[(2-methanesulphonyl-ethyl)amino]methyl}-furan-2-yl)quinazoline
- 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-methoxy-quinazoline
- 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]-amino}-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline
- 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N,N-to-(2-methoxy-ethyl)-amino]-1-oxo-2-buten-1-yl}amino)-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline
- 4-[(3-ethynyl-phenyl)amino]-6-{[4-(5.5-dimethyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-methoxy-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-[(R)-(tetrahydrofuran-2-yl)methoxy]-quinazoline

- 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-6-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{2-[4-(2-oxo-morpholin-4-yl)-piperidin-1-yl]-ethoxy}-7-methoxy-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(tert.-butyloxycarbonyl)-piperidin-4-yloxy]-7-methoxy-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-amino-cyclohexan-1-yloxy)-7-methoxy-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methanesulphonylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-3-yloxy)-7-methoxy-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7-methoxy-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(methoxymethyl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(piperidin-3-yloxy)-7-methoxy-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(2-acetylamino-ethyl)-piperidin-4-yloxy]-7-methoxy-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-ethoxy-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-((S)-tetrahydrofuran-3-yloxy)-7-hydroxy-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-(2-methoxy-ethoxy)-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{trans-4-[(dimethylamino)sulphonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{trans-4-[(morpholin-4-yl)carbonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline

- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{trans-4-[(morpholin-4-yl)sulphonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-(2-acetylamino-ethoxy)-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-(2-methanesulphonylamino-ethoxy)-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(piperidin-1-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-aminocarbonylmethyl-piperidin-4-yloxy)-7-methoxy-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(tetrahydropyran-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(morpholin-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(morpholin-4-yl)sulphonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy- quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-ethanesulphonylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-ethoxy-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-(2-methoxy-ethoxy)-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(2-methoxy-acetyl)-piperidin-4-yloxy]-7-(2-methoxy-ethoxy)-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-acetylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline
- 4-[(3-ethynyl-phenyl)amino]-6-[1-(tert.-butyloxycarbonyl)-piperidin-4-yloxy]-7-methoxy-quinazoline
- 4-[(3-ethynyl-phenyl)amino]-6-(tetrahydropyran-4-yloxy]-7-methoxy-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(piperidin-1-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline

- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(4-methyl-piperazin-1-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{cis-4-[(morpholin-4-yl)carbonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[2-(2-oxopyrrolidin-1-yl)ethyl]-piperidin-4-yloxy}-7-methoxy-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-(2-methoxy-ethoxy)-quinazoline
- 4-[(3-ethynyl-phenyl)amino]-6-(1-acetyl-piperidin-4-yloxy)-7-methoxy-quinazoline
- 4-[(3-ethynyl-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7-methoxy-quinazoline
- 4-[(3-ethynyl-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-methoxy-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7(2-methoxy-ethoxy)-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-isopropyloxycarbonyl-piperidin-4-yloxy)-7-methoxy-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-methylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{cis-4-[N-(2-methoxy-acetyl)-N-methyl-amino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline
- 4-[(3-ethynyl-phenyl)amino]-6-(piperidin-4-yloxy)-7-methoxy-quinazoline
- 4-[(3-ethynyl-phenyl)amino]-6-[1-(2-methoxy-acetyl)-piperidin-4-yloxy]-7-methoxy-quinazoline
- 4-[(3-ethynyl-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(cis-2,6-dimethyl-morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(2-methyl-morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline

- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(S,S)-(2-oxa-5-aza-bicyclo[2,2,1]hept-5-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(N-methyl-N-2-methoxyethyl-amino)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-ethyl-piperidin-4-yloxy)-7-methoxy-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(2-methoxyethyl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(3-methoxypropyl-amino)-carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(N-methanesulphonyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(N-acetyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[trans-4-(N-methanesulphonyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-dimethylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-{N-[(morpholin-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-methoxy-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-cyano-piperidin-4-yloxy)-7-methoxy-quinazoline

optionally in the form of the racemates, enantiomers, diastereomers thereof and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof. According to the invention the acid addition salts of the betamimetics are preferably selected from among the hydrochloride, hydrobromide,

hydriodide, hydrosulphate, hydrophosphate, hydromethanesulphonate, hydronitrate, hydromaleate, hydroacetate, hydrocitrate, hydrofumarate, hydrotartrate, hydroxalate, hydrosuccinate, hydrobenzoate and hydro-p-toluenesulphonate.

The dopamine agonists used are preferably compounds selected from among bromocriptin, cabergoline, alpha-dihydroergocryptine, lisuride, pergolide, pramipexol, roxindol, ropinirol, talipexol, tergurid and viozan, optionally in the form of the racemates, enantiomers, diastereomers thereof and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof. According to the invention the acid addition salts of the betamimetics are preferably selected from among the hydrochloride, hydrobromide, hydriodide, hydrosulphate, hydrophosphate, hydromethanesulphonate, hydronitrate, hydromaleate, hydroacetate, hydrocitrate, hydrofumarate, hydrotartrate, hydrooxalate, hydrosuccinate, hydrobenzoate and hydro-p-toluenesulphonate.

H1-Antihistamines which may be used are preferably compounds selected from among epinastine, cetirizine, azelastine, fexofenadine, levocabastine, loratadine, mizolastine, ketotifen, emedastine, dimetindene, clemastine, bamipine, cexchlorpheniramine, pheniramine, doxylamine, chlorophenoxamine, dimenhydrinate, diphenhydramine, promethazine, ebastine, desloratidine and meclozine, optionally in the form of the racemates, enantiomers, diastereomers thereof and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof. According to the invention the acid addition salts of the betamimetics are preferably selected from among the hydrochloride, hydrobromide, hydriodide, hydrosulphate, hydrophosphate, hydromethanesulphonate, hydronitrate, hydromaleate, hydroacetate, hydrocitrate, hydrofumarate, hydrotartrate, hydroxalate, hydrosuccinate, hydrobenzoate and hydro-p-toluenesulphonate.

In addition, inhalable macromolecules as disclosed in EP 1 003 478 A1 or CA 2297174 A1 may also be used.

In addition, the compound may be selected from among the ergot alkaloid derivatives, the triptans, the CGRP-inhibitors, the phosphodiesterase-V inhibitors, optionally in the form of the racemates, enantiomers or diastereomers thereof, optionally in the form of the pharmacologically acceptable acid addition salts, the solvates and/or hydrates thereof.

Examples of ergot alkaloid derivatives are dihydroergotamine and ergotamine.

List of reference numerals

1	inhaler
2	medicament preparation
3	container
4	bag
5	pressure generator
6	holder
7	drive spring
8	locking element
9	conveying tube
10	non-return valve
11	pressure chamber
12	delivery nozzle
13	mouthpiece
14	aerosol
15	supply air opening
16	first housing part (upper part)
17	inner part
17a	upper part of the inner part
17b	lower part of the inner part
18	second housing part (lower part)
19	retaining element
20	spring (in the lower housing part)
21	container base
22	piercing element
23	add-on device
24	chamber
25	housing
26	connecting member
27	delivery member
28	valve
29	add-on mouthpiece
30	tube
31	face mask
32	valve

Claims:

1. Portable inhaler for the propellant-free nebulisation of a medicament preparation, having a pressure generator preferably constructed as a pump and/or operating mechanically, and having a delivery nozzle for delivering the nebulised medicament preparation as an aerosol into a mouthpiece,

wherein the inhaler has an add-on device with a chamber for intermediate storage of the aerosol,

wherein the chamber is arranged or adapted to be arranged downstream of the delivery nozzle, and

wherein the mouthpiece has at least one supply air opening which remains open when the add-on device is attached, particularly pushed on.

2. Inhaler according to claim 1, wherein the add-on device can be fitted onto the mouthpiece preferably by clamping and/or is removable from the inhaler or mouthpiece.

3. Inhaler according to claim 1 or 2, wherein the add-on device or the chamber is at least substantially cylindrical, elongate or conical in construction.

4. Inhaler according to one of the preceding claims, wherein the chamber has a volume of more than at least 0.1 l, preferably more than 0.2 l, more particularly of about 0.2 to 0.6 l.

5. Inhaler according to one of the preceding claims, wherein the add-on device comprises in particular at the delivery end a valve for preventing air from flowing back into the chamber and/or the mouthpiece and/or for sucking in the aerosol and/or at least one valve for blowing out exhaled air.

6. Inhaler according to one of the preceding claims, wherein the add-on device is equipped or adapted to be equipped preferably selectively with an add-on mouthpiece, a tube and/or a face mask.

7. Inhaler according to one of the preceding claims, wherein the inhaler is constructed so that the aerosol is expelled at low speed, particularly at a speed of less than 2 m/s, particularly preferably of about 1.6 m/s or less, at a spacing of 10 cm from the delivery nozzle.

8. Inhaler according to one of the preceding claims, wherein the inhaler is constructed so that it delivers and nebulises 10 to 50 µl of the medicament preparation over a period of at least 1 s, particularly over 1.5 s, on each actuation or as the dose.

9. Inhaler according to one of the preceding claims, wherein the inhaler is constructed so as to nebulise defined amounts of the medicament preparation under pressures of 10 to 60 MPa.

10. Inhaler according to one of the preceding claims, wherein the pressure generation or nebulisation is carried out by spring force.

11. Use of an add-on device with a chamber in a portable inhaler, wherein the inhaler is designed for propellant-free nebulisation of a medicament preparation by means of a pressure generator constructed as a pump, wherein the inhaler has a delivery nozzle for delivering the nebulised medicament preparation as an aerosol into a mouthpiece with at least one supply air opening and wherein the medicament preparation can be delivered through the delivery nozzle as an aerosol, the add-on device being connected to the inhaler in such way that the chamber is connected to the inhaler downstream of the delivery nozzle for intermediate storage of the nebulised medicament preparation and that the at least one supply air opening of the mouthpiece remains open when the add-on device is connected to the inhaler.