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PRODUCTION OF A MEDICAMENT(54) Bezeichnung: KRISTALLINES MONOHYDRAT, VERFAHREN ZU DESSEN HERSTELLUNG UND DESSEN VERWEN-
DUNG ZUR HERSTELLUNG EINES ARZNEIMITTELS(57) Abstract: The invention relates to a crystalline monohydrate of (1 α ,2 β ,4 β ,5 α ,7 β)-7-[(hydroxydi-2-thienylacetyl)oxy]-9,9-
dimethyl-3-oxa-9-azoniatrycyclo[3.3.1.0^{2,4}]nonane bromide, to a method for producing the same, and to the use thereof in the pro-
duction of a medicament, especially for producing a medicament that has an anticholinergic effect.(57) Zusammenfassung: Die Erfindung betrifft ein kristallines Monohydrat von (1 α ,2 β ,4 β ,5 α ,7 β)-7-[(hydroxydi-2-thienyl-
acetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatrycyclo[3.3.1.0^{2,4}]nonan-bromid, Verfahren zu dessen Herstellung, sowie dessen
Verwendung zur Herstellung eines Arzneimittels, insbesondere zur Herstellung eines Arzneimittels mit anticholinergischer Wirkung.

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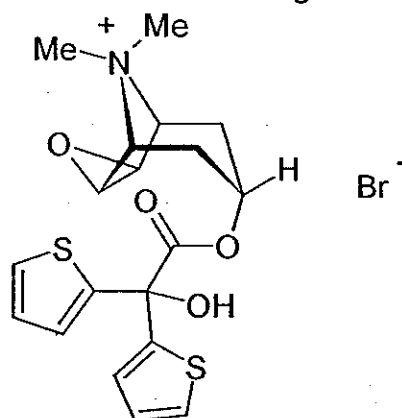
Crystalline monohydrate, processes for the preparation thereof and the use thereof for preparing a pharmaceutical composition

- 5 The invention relates to a crystalline monohydrate of $(1\alpha,2\beta,4\beta,5\alpha,7\beta)$ -7-[(hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.0^{2,4}]nonane-bromide, processes for the preparation thereof, as well as the use thereof for preparing a pharmaceutical composition, particularly for preparing a pharmaceutical composition having an anticholinergic activity.

10

Background to the invention

The compound $(1\alpha,2\beta,4\beta,5\alpha,7\beta)$ -7-[(hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.0^{2,4}]nonane-bromide is known from European Patent Application EP 418 716 A1 and has the following chemical structure:



(I)

15

The compound has valuable pharmacological properties and is known by the name tiotropium bromide (BA679). Tiotropium bromide is a highly effective anticholinergic and can therefore provide therapeutic benefit in the treatment of asthma or COPD (chronic obstructive pulmonary disease).

20

Tiotropium bromide is preferably administered by inhalation. Suitable inhalable powders packed into appropriate capsules (inhalettes) may be used. Alternatively, it may be administered by the use of suitable inhalable aerosols. These also include powdered inhalable aerosols which contain, for example, HFA134a, HFA227 or

25

The correct manufacture of the abovementioned compositions which are suitable for use for the administration of a pharmaceutically active substance by inhalation is based on various parameters which are connected with the nature of the active substance itself. Without being restrictive, examples of these parameters are the

30

stability of effect of the starting material under various environmental conditions,

stability during production of the pharmaceutical formulation and stability in the final medicament compositions. The pharmaceutically active substance used for preparing the abovementioned pharmaceutical compositions should be as pure as possible and its stability in long-term storage must be guaranteed under various

5 environmental conditions. This is absolutely essential to prevent the use of pharmaceutical compositions which contain, in addition to the actual active substance, breakdown products thereof, for example. In such cases the content of active substance in the capsules might be less than that specified.

The absorption of moisture reduces the content of pharmaceutically active substance
10 on account of the weight gain caused by the uptake of water. Pharmaceutical compositions with a tendency to absorb moisture have to be protected from damp during storage, e.g. by the addition of suitable drying agents or by storing the medicament in a damp-proof environment. In addition, the uptake of moisture can reduce the content of pharmaceutically active substance during manufacture if the
15 medicament is exposed to the environment without being protected from damp in any way.

Uniform distribution of the medicament in the formulation is a critical factor, particularly when the medicament has to be given in low doses. To ensure uniform
20 distribution, the particle size of the active substance can be reduced to a suitable level, e.g. by grinding. Another aspect which is important in active substances to be administered by inhalation, e.g. by means of a powder, arises from the fact that only particles of a certain size can be taken into the lungs by inhalation. The particle size of these lung-bound particles (inhalable fraction) is in the sub-micron range. In order
25 to obtain active substances of a corresponding particle size, a grinding process (so-called micronising) is again required.

Since breakdown of the pharmaceutically active substance as a side effect of the grinding (or micronising) has to be avoided as far as possible, in spite of the hard
30 conditions required during the process, it is absolutely essential that the active substance should be highly stable throughout the grinding process. Only if the active substance is sufficiently stable during the grinding process is it possible to produce a homogeneous pharmaceutical formulation which always contains the specified amount of active substance in reproducible manner.

35

Another problem which may arise in the grinding process for preparing the desired pharmaceutical formulation is the input of energy caused by this process and the stress on the surface of the crystals. This may in certain circumstances lead to polymorphous changes, to a change in the amorphous configuration or to a change

in the crystal lattice. Since the pharmaceutical quality of a pharmaceutical formulation requires that the active substance should always have the same crystalline morphology, the stability and properties of the crystalline active substance are subject to stringent requirements from this point of view as well.

5

The stability of a pharmaceutically active substance is also important in pharmaceutical compositions for determining the shelf life of the particular medicament; the shelf life is the length of time during which the medicament can be administered without any risk. High stability of a medicament in the abovementioned
10 pharmaceutical compositions under various storage conditions is therefore an additional advantage for both the patient and the manufacturer.

Apart from the requirements indicated above, it should be generally borne in mind that any change to the solid state of a pharmaceutical composition which is capable
15 of improving its physical and chemical stability gives a significant advantage over less stable forms of the same medicament.

The aim of the invention is thus to provide a new, stable crystalline form of the compound tiotropium bromide which meets the stringent requirements imposed on
20 pharmaceutically active substances as mentioned above.

Detailed description of the invention

It has been found that, depending on the choice of conditions which can be used when purifying the crude product obtained after industrial manufacture, tiotropium
25 bromide occurs in various crystalline modifications.

It has been found that these different modifications can be deliberately produced by selecting the solvents used for the crystallisation as well as by a suitable choice of the process conditions used in the crystallisation process.

30

Surprisingly, it has been found that the monohydrate of tiotropium bromide, which can be obtained in crystalline form by choosing specific reaction conditions, meets the stringent requirements mentioned above and thus solves the problem on which the present invention is based. Accordingly, a first aspect of the present invention provides
35 a crystalline tiotropium bromide monohydrate.

3a

According to a second aspect of the present invention, there is provided a process for preparing crystalline hydrates of tiotropium bromide characterised in that tiotropium bromide is taken up in water, the mixture obtained is heated and finally the hydrates of tiotropium bromide are crystallised with slow cooling. The tiotropium bromide may be obtained for example by the method

disclosed in EP 418716 A1.

A third aspect of the present invention further provides crystalline hydrates of tiotropium bromide, obtainable by the process as defined above.

A fourth aspect of the present invention provides a process for preparing crystalline tiotropium bromide monohydrate as defined above, characterised in that

- a) tiotropium bromide is taken up in water,
- b) the mixture obtained is heated,
- c) activated charcoal is added and
- d) after the removal of the activated charcoal, tiotropium bromide monohydrate is slowly crystallised with slow cooling of the aqueous solution. The tiotropium bromide may be obtained for example according to the method disclosed in EP 418716 A1.

The method described below is preferably used according to the invention.

In a suitably dimensioned reaction vessel the solvent is mixed with tiotropium bromide, which has been obtained for example according to the method disclosed in EP 418 716 A1.

0.4 to 1.5 kg, preferably 0.6 to 1 kg, most preferably about 0.8 kg of water are used as solvent per mole of tiotropium bromide used. The mixture obtained is heated with stirring, preferably to more than 50°C, most preferably to more than 60°C. The maximum temperature which can be selected will be determined by the boiling point of the solvent used, i.e. water. Preferably the mixture is heated to a range from 80-90°C.

Activated charcoal, dry or moistened with water, is added to this solution. 10 to 50 g, more preferably 15 to 35 g, most preferably about 25 g of activated charcoal are put in per mole of tiotropium bromide used. If desired, the activated charcoal is suspended in water before being added to the solution containing the tiotropium bromide. 70 to 200 g, preferably 100 to 160 g, most preferably about 135 g water are used to suspend the activated charcoal, per mole of tiotropium bromide used. If the activated charcoal is suspended in water prior to being added to the solution containing the tiotropium bromide, it is advisable to rinse with the same amount of water.

After the activated charcoal has been added, stirring is continued at constant temperature for between 5 and 60 minutes, preferably between 10 and 30 minutes, most preferably about 15 minutes, and the mixture obtained is filtered to remove the activated charcoal. The filter is then rinsed with water. 140 to 400 g, preferably 200 to 320 g, most preferably about 270 g of water are used for this, per mole of tiotropium bromide used.

The filtrate is then slowly cooled, preferably to a temperature of 20-25°C. The cooling is preferably carried out at a cooling rate of 1 to 10°C per 10 to 30 minutes, preferably 2 to 8°C per 10 to 30 minutes, more preferably 3 to 5°C per 10 to 20 minutes, most preferably 3 to 5°C roughly per 20 minutes. If desired, the cooling to
5 20 to 25°C may be followed by further cooling to below 20°C, most preferably to 10 to 15°C.

Once the filtrate has cooled, it is stirred for between 20 minutes and 3 hours, preferably between 40 minutes and 2 hours, most preferably about one hour, to
10 complete the crystallisation.

The crystals formed are finally isolated by filtering or suction filtering the solvent. If it proves necessary to subject the crystals obtained to another washing step, it is advisable to use water or acetone as the washing solvent. 0.1 to 1.0 l, preferably 0.2
15 to 0.5 l, most preferably about 0.3 l solvent are used, per mole of tiotropium bromide, to wash the tiotropium bromide monohydrate crystals obtained. If desired the washing step may be repeated.

The product obtained is dried *in vacuo* or using circulating hot air until a water content of 2.5 – 4.0 % is obtained.

20

The crystalline tiotropium bromide monohydrate defined in the first aspect can be obtained using the method described above.

The tiotropium bromide monohydrate obtainable using the method described above
25 was investigated by DSC (Differential Scanning Calorimetry). The DSC diagram shows two characteristic signals. The first, relatively broad, endothermic signal between 50-120°C can be attributed to the dehydration of the tiotropium bromide monohydrate into the anhydrous form. The second, relatively sharp, endothermic peak at $230 \pm 5^\circ\text{C}$ can be put down to the melting of the substance (Figure 1). This
30 data was obtained using a Mettler DSC 821 and evaluated using the Mettler STAR software package. The data was recorded at a heating rate of 10 K/min.

Since the substance melts with decomposition (= incongruent melting process), the melting point observed depends to a great extent on the heating rate. At lower
35 heating rates, the melting/decomposition process is observed at significantly lower temperatures, e.g. at $220 \pm 5^\circ\text{C}$ with a heating rate of 3 K/min. It is also possible that the melting peak may be split. The split is all the more apparent the lower the heating rate in the DSC experiment.

The present invention is therefore directed to crystalline tiotropium bromide monohydrate which is characterised, according to Figure 1, by an endothermic peak at 230°C ($\pm 5^\circ\text{C}$) at a heating rate of 10 K/min.

- 5 The tiotropium bromide monohydrate according to the invention was characterised by IR spectroscopy. The data was obtained using a Nicolet FTIR spectrometer and evaluated with the Nicolet OMNIC software package, version 3.1. The measurement was carried out with 2.5 μmol of tiotropium bromide monohydrate in 300 mg of KBr. The IR spectrum obtained is shown in Figure 2.
- 10 Table 1 shows some of the essential bands of the IR spectrum.

Table 1: Attribution of specific bands

Wave number (cm^{-1})	Attribution	Type of oscillation
3570, 410	O-H	elongated oscillation
3105	Aryl C-H	elongated oscillation
1730	C=O	elongated oscillation
1260	Epoxide C-O	elongated oscillation
1035	Ester C-OC	elongated oscillation
720	Thiophene	cyclic oscillation

- 15 Accordingly, the present invention relates to crystalline tiotropium bromide monohydrate which is characterised according to Figure 2 by an IR spectrum which has bands at wave numbers 3570, 3410, 3105, 1730, 1260, 1035 and 720 cm^{-1} , *inter alia*.
- 20 The tiotropium bromide monohydrate according to the invention was characterised by X-ray structural analysis. The measurements of X-ray diffraction intensity were carried out on an AFC7R- 4-circuit diffractometer (Rigaku) using monochromatic copper K_α radiation. The structural solution and refinement of the crystal structure were obtained by direct methods (SHELXS86 Program) and FMLQ-refinement
- 25 (TeXsan Program). Experimental details of the crystalline structure, structural resolution and refinement are collected in Table 2.

Table 2: Experimental data on the analysis of the crystalline structure of tiotropium bromide monohydrate.

A. Crystal data

	Empirical formula	$[\text{C}_{19}\text{H}_{22}\text{NO}_4\text{S}_2] \text{ Br} \cdot \text{H}_2\text{O}$
5	Weight of formula	472.43 + 18.00
	colour and shape of crystals	colourless, prismatic
	dimensions of crystals	0.2 x 0.3 x 0.3 mm
	crystal system	monoclinic
	lattice type	primitive
10	space group	$P 2_1/n$
	lattice constants	$a = 18.0774 \text{ \AA}$, $b = 11.9711 \text{ \AA}$ $c = 9.9321 \text{ \AA}$ $\beta = 102.691^\circ$
15		$V = 2096.96 \text{ \AA}^3$
	formula units per elementary cell	4

B. Measurements of intensity

	Diffractometer	Rigaku AFC7R
20	X-ray generator	Rigaku RU200
	wavelength	$\lambda = 1.54178 \text{ \AA}$ (monochromatic copper K_α -radiation)
	current, voltage	50kV, 100mA
	take-off angle	6°
25	crystal assembly	steam-saturated capillary
	crystal-detector gap	235mm
	detector opening	3.0 mm vertical and horizontal
	temperature	18°
	determining the lattice constants	25 reflexes ($50.8^\circ < 2\theta < 56.2^\circ$)
30	Scan Type	$\omega - 2\theta$
	Scan speed	$8.0 \text{ } 32.0^\circ/\text{min}$ in ω
	Scan width	$(0.58 + 0.30 \tan \Theta)^\circ$
	$2\theta_{\text{max}}$	120°
	measured	5193
35	independent reflexes	3281 ($R_{\text{int}}=0.051$)
	corrections	Lorentz polarisation Absorption (Transmission factors 0.56 – 1.00) crystal decay 10.47% decay

C. Refinement

	Reflections ($I > 3\sigma I$)	1978
	Variable	254
5	ratio of reflections/parameters	7.8
	R-values: R, Rw	0.062, 0.066

The X-ray structural analysis carried out showed that crystalline tiotropium bromide hydrate has a simple monoclinic cell with the following dimensions:

10 $a = 18.0774 \text{ \AA}$, $b = 11.9711 \text{ \AA}$, $c = 9.9321 \text{ \AA}$, $\beta = 102.691^\circ$, $V = 2096.96 \text{ \AA}^3$.

Accordingly, the present invention relates to crystalline tiotropium bromide monohydrate which is characterised by the elementary cell described above.

The atomic coordinates described in Table 3 were determined by the above X-ray structural analysis:

15

Table 3: Coordinates

	Atom	x	y	z	u (eq)
	Br(1)	0.63938(7)	0.0490(1)	0.2651(1)	0.0696(4)
20	S(1)	0.2807(2)	0.8774(3)	0.1219(3)	0.086(1)
	S(2)	0.4555(3)	0.6370(4)	0.4214(5)	0.141(2)
	O(1)	0.2185(4)	0.7372(6)	0.4365(8)	0.079(3)
	O(2)	0.3162(4)	0.6363(8)	0.5349(9)	0.106(3)
	O(3)	0.3188(4)	0.9012(5)	0.4097(6)	0.058(2)
25	O(4)	0.0416(4)	0.9429(6)	0.3390(8)	0.085(3)
	O(5)	0.8185(5)	0.0004(8)	0.2629(9)	0.106(3)
	N(1)	0.0111(4)	0.7607(6)	0.4752(7)	0.052(2)
	C(1)	0.2895(5)	0.7107(9)	0.4632(9)	0.048(3)
	C(2)	0.3330(5)	0.7876(8)	0.3826(8)	0.048(3)
30	C(3)	0.3004(5)	0.7672(8)	0.2296(8)	0.046(3)
	C(4)	0.4173(5)	0.7650(8)	0.4148(8)	0.052(3)
	C(5)	0.1635(5)	0.6746(9)	0.497(1)	0.062(3)
	C(6)	0.1435(5)	0.7488(9)	0.6085(9)	0.057(3)
	C(7)	0.0989(6)	0.6415(8)	0.378(1)	0.059(3)
35	C(8)	0.0382(5)	0.7325(9)	0.3439(9)	0.056(3)
	C(9)	0.0761(6)	0.840(1)	0.315(1)	0.064(3)
	C(10)	0.1014(6)	0.8974(8)	0.443(1)	0.060(3)
	C(11)	0.0785(5)	0.8286(8)	0.5540(9)	0.053(3)
	C(12)	-0.0632(6)	0.826(1)	0.444(1)	0.086(4)

continuation of Table 3: Coordinates

	Atom	x	y	z	u (eq)
5	C(13)	-0.0063(6)	0.6595(9)	0.554(1)	0.062(3)
	C(14)	0.4747(4)	0.8652(9)	0.430(1)	0.030(2)
	C(15)	0.2839(5)	0.6644(9)	0.1629(9)	0.055(3)
	C(16)	0.528(2)	0.818(2)	0.445(2)	0.22(1)
	C(17)	0.5445(5)	0.702(2)	0.441(1)	0.144(6)
10	C(18)	0.2552(6)	0.684(1)	0.019(1)	0.079(4)
	C(19)	0.2507(6)	0.792(1)	-0.016(1)	0.080(4)
	H(1)	-0.0767	0.8453	0.5286	0.102
	H(2)	-0.0572	0.8919	0.3949	0.102
	H(3)	-0.1021	0.7810	0.3906	0.102
15	H(4)	-0.0210	0.6826	0.6359	0.073
	H(5)	-0.0463	0.6178	0.4982	0.073
	H(6)	0.0377	0.6134	0.5781	0.073
	H(7)	0.1300	0.7026	0.6770	0.069
	H(8)	0.1873	0.7915	0.6490	0.069
20	H(9)	0.1190	0.6284	0.2985	0.069
	H(10)	0.0762	0.5750	0.4016	0.069
	H(11)	0.1873	0.6082	0.5393	0.073
	H(12)	-0.0025	0.7116	0.2699	0.066
	H(13)	0.1084	0.8383	0.2506	0.075
25	H(14)	0.1498	0.9329	0.4626	0.071
	H(15)	0.0658	0.8734	0.6250	0.063
	H(16)	0.2906	0.5927	0.2065	0.065
	H(17)	0.2406	0.6258	-0.0469	0.094
	H(18)	0.2328	0.8191	-0.1075	0.097
30	H(19)	0.4649	0.9443	0.4254	0.037
	H(20)	0.5729	0.8656	0.4660	0.268
	H(21)	0.5930	0.6651	0.4477	0.165
	H(22)	0.8192	-0.0610	0.1619	0.084
	H(23)	0.7603	0.0105	0.2412	0.084

x, y, z: fractional coordinates;

35 U(eq) mean quadratic amplitude of atomic movement in the crystal;

The present invention relates to the use of tiotropium

bromide monohydrate as a medicament in the light of the pharmaceutical efficacy of the hydrate according to the invention.

9a

- Accordingly, a fifth aspect of the present invention provides a medicament, characterised in that it contains crystalline tiotropium bromide monohydrate as defined above.

To prepare a medicament which can be inhaled, particularly an inhalable powder, which contains the crystalline tiotropium bromide monohydrate described by the present invention, methods known from the prior art may be used. In this respect, reference is made, for example, to the teaching of DE-A-179 22 07. Accordingly,

5 the present invention relates to inhalable powders characterised in that they contain tiotropium bromide monohydrate.

In view of the anticholinergic effects of tiotropium bromide monohydrate a sixth aspect of the present invention provides a use of crystalline tiotropium bromide monohydrate as defined
10 above for preparing a pharmaceutical composition for treating diseases in which the administration of an anticholinergic agent may have a therapeutic benefit. It is preferably used for preparing a pharmaceutical composition for treating asthma or COPD.

The following example of synthesis serves to illustrate a method of preparing
15 crystalline tiotropium bromide monohydrate carried out by way of example. It is to be regarded only as a possible method described by way of example, without restricting the invention to its contents.

Example of synthesis

In a suitable reaction vessel 15.0 kg of tiotropium bromide are added to 25.7 kg of
20 water. The mixture is heated to 80-90°C and stirred at constant temperature until a clear solution is formed. Activated charcoal (0.8 kg), moistened with water, is suspended in 4.4 kg of water, this mixture is added to the solution containing the tiotropium bromide and rinsed with 4.3 kg of water. The mixture thus obtained is stirred for at least 15 min at 80-90°C and then filtered through a heated filter into an
25 apparatus which has been preheated to an outer temperature of 70°C. The filter is rinsed with 8.6 kg of water. The contents of the apparatus are cooled to a temperature of 20-25°C at a rate of 3-5°C per 20 minutes. The apparatus is further cooled to 10-15°C using cold water, and the crystallisation is completed by stirring for at least one hour. The crystals are isolated using a suction filter drier, the crystal
30 slurry isolated is washed with 9 l of cold water (10-15°C) and cold acetone (10-15°C). The crystals obtained are dried at 25°C for 2 hours in a nitrogen current.
Yield : 13.4 kg of tiotropium bromide monohydrate (86 % of theory)

Patent Claims

- 1) Crystalline tiotropium bromide monohydrate.
- 5 2) Crystalline tiotropium bromide monohydrate according to claim 1, characterised by an endothermic peak at $230 \pm 5^\circ\text{C}$ occurring during thermal analysis using DSC, at a heating rate of 10K/min.
- 10 3) Crystalline tiotropium bromide monohydrate according to claim 1 or 2, characterised by an IR spectrum which comprises bands at wave numbers 3570, 3410, 3105, 1730, 1260, 1035 and 720 cm^{-1} , *inter alia*.
- 15 4) Crystalline tiotropium bromide monohydrate according to one of claims 1, 2 or 3, characterised by a single monoclinic cell having the following dimensions: $a = 18.0774\text{ \AA}$, $b = 11.9711\text{ \AA}$, $c = 9.9321\text{ \AA}$, $\beta = 102.691^\circ$, $V = 2096.96\text{ \AA}^3$.
- 20 5) Process for preparing crystalline tiotropium bromide monohydrate according to one of claims 1, 2, 3 or 4, characterised in that
 - a) tiotropium bromide is taken up in water,
 - b) the mixture obtained is heated,
 - c) activated charcoal is added and
 - d) after the removal of the activated charcoal, tiotropium bromide monohydrate is slowly crystallised with slow cooling of the aqueous solution.
- 25 6) Process according to claim 5, characterised in that
 - a) 0.4 to 1.5 kg of water are used per mole of tiotropium bromide put in,
 - b) the mixture obtained is heated to more than 50°C ,
 - c) 10 to 50 g of activated charcoal are used per mole of tiotropium bromide used and after the activated charcoal has been added stirring is continued for between 5 and 60 minutes,
 - d) the mixture obtained is filtered, the filtrate obtained is cooled to a temperature of $20\text{-}25^\circ\text{C}$ at a cooling rate of $1\text{ to }10^\circ\text{C}$ per 10 to 30 minutes and the tiotropium bromide monohydrate is thus crystallised.
- 30 7) Medicament, characterised in that it contains crystalline tiotropium bromide monohydrate according to one of claims 1 to 4.
- 15 8) Medicament according to claim 7, characterised in that it is an

inhalable powder.

- 5 9) Use of crystalline tiotropium bromide monohydrate according to one of claims 1 to 4 for preparing a pharmaceutical composition for treating diseases in which the administration of an anticholinergic agent may have a therapeutic benefit.
- 10) Use according to claim 9, characterised in that the diseases are asthma or COPD.
- 10 11) Process for preparing crystalline hydrates of tiotropium bromide, characterised in that tiotropium bromide is taken up in water, the mixture obtained is heated and finally the hydrates of tiotropium bromide are crystallised with slow cooling.
- 15 12) Crystalline hydrates of tiotropium bromide, obtainable by the process according to claim 11.