

GALENIC COMPOSITIONS COMPRISING CALCITONIN AND THEIR USE

The present invention relates to novel galenic compositions comprising a calcitonin as active ingredient.

5 The calcitonins comprise a known class of pharmaceutically active, long-chain polypeptides of varying, well documented pharmaceutical utility. Various calcitonins, including e.g. salmon and eel calcitonin, are commercially available and commonly employed in the treatment of e.g. Paget's disease, hypercalcaemia and osteoporosis.

10 As is commonly the case with polypeptides however, provision of convenient and effective means of administering calcitonins has presented many difficulties. Being polypeptides, the calcitonins are susceptible to degradation on administration and only pass with difficulty into the body fluids. For this reason parenteral
15 administration has hitherto been the only route commonly available which permits effective treatment. Generally administration is by injection. Such means of administration are always inconvenient and when administration is to be effected at regular intervals can cause considerable pain to the patient. The finding of viable
20 alternative means of administration causing less discomfort to the patient and preferably allowing ready self-application while at the same time achieving bio-availability levels sufficient for effective treatment in clinic has accordingly remained, for many years, a major goal.

We have now found that it is possible to provide effective clinical treatment with calcitonins by administration via the nasal route, i.e. by application to the nasal mucosa. More particularly we have found that in accordance with the particular teachings of the present invention, calcitonin bio-availability levels equivalent to those obtained on administration of standard intra-muscular doses can be achieved on nasal administration at dosage levels which are fully within the limits of tolerability and practicability. It has further been found that the fish calcitonins and their derivatives e.g. salmon calcitonin and the eel calcitonin derivative 1,7-Asu-eel calcitonin, herein referred to as Elcatonin, and in particular salmon calcitonin, are especially suited for application via the nasal route in accordance with the teachings of the invention.

15 The nasal route provides a simple and painless mode of administration which may be easily carried out by the patient himself, for example administering a nasal spray or drop solution from a nasal applicator. This route is clearly of great advantage over parenteral administration which has generally to be given under
20 medical supervision.

While administration via the nasal route will clearly be preferable to parenteral administration, e.g. injection, as hitherto commonly practiced, the provision of a composition suitable for use for a nasal dosage form itself presents many difficulties.

25 One problem, especially acute in relation to nasal administration of complex pharmaceutical agents such as the calcitonins, is that of providing a fully compatible and effective means for avoiding contamination e.g. by pathogenic or other undesired micro-organisms. Provision of an appropriate active-ingredient-compatible and effective
30 preserving agent to protect against contamination is especially critical for a nasal pharmaceutical composition where the risk of contamination is particularly high. The preserving agent must

suffice to provide not only for initial contamination avoidance, e.g. during formulation and filling of the composition into its container, but continued contamination avoidance during use particularly where multiple dosaging from a single container/applicator is required. In particular problems arise where e.g. a nasal applicator is, as is often the case, subsequently stored for months before use. During this phase the selected preserving agent may be rendered useless, e.g. by absorption onto the inside surfaces of the applicator, by heat-degradation, or, where the preserving agent is to any degree unduly volatile, as a consequence of leakage from the applicator. Further, during the actual phase of use (and where multiple dosaging from a single applicator is foreseen this may extend over a period of several days or weeks), there is danger that the applicator may leak or otherwise let in unwanted micro-organisms or other contaminants from the outside atmosphere generally, or from the nostrils. Moreover the composition may be subjected to brief periods of elevated temperature, e.g. during transport or storage.

In addition to the above mentioned difficulties a pharmaceutical composition developed for nasal application must at the same time be appropriately tolerated in particular at the immediate site of application. It should, for example, neither cause irritation to the nasal mucosa (e.g. should cause no significant prickling sensation) nor cause significant reduction of the ciliary beating frequency.

Very many well-known preserving agents present themselves for possible use in calcitonin pharmaceutical compositions. However experiment has shown that not all are suitable for practical use in relation to a calcitonin nasal spray. Thus chlorbutanol at 0.6% in calcitonin nasal pharmaceutical compositions showed insufficient activity against the test fungus *Pen. steckii*, more than

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3-days being required to reduce the cell count to less than 0.1%. Moreover, chlorbutanol was found to attack rubber stoppers and other joints used in nasal spray applicators between the spray pump and a bottle.

5 Chlorbutanol additionally caused at 0.6% more than 50% inhibition of the ciliary beating frequency of rat trachea within 20 minutes according to the microphoto-oscillographic method of L. Chevance et al, Acta Otolaryng. 70, 16:28 (1970). These are just some of the disadvantageous effects that can be encountered.

10 In accordance with the present invention it has now been surprisingly found that pharmaceutical compositions can be obtained comprising a calcitonin as active ingredient which meet the high standards of stability and tolerability required for nasal application and which are, for example, eminently suitable for use in multiple
15 dose nasal spray applicators, i.e. applicators capable of delivering a series of individual dosages over e.g. period of several days or weeks, by the use of benzalkonium chloride as a co-ingredient and preserving agent. Surprisingly it has also been found that use of benzalkonium chloride, even at the very low concentration
20 required for use as a preserving agent, may confer beneficial advantages in relation to the nasal resorption characteristics of calcitonin containing compositions and hence enhance calcitonin bio-availability levels consequential to nasal application.

In accordance with the foregoing the present invention provides,
25 in a first aspect, a pharmaceutical composition for nasal administration, comprising:

- i) a calcitonin, and
- ii) benzalkonium chloride, in
- iii) a liquid diluent or carrier, suitable for application
30 to the nasal mucosa.

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The term "calcitonin" is used throughout the present specification and claims in a broad sense to include not only the naturally occurring calcitonins, but also their pharmaceutically active derivatives and analogues, e.g. in which one or more of the peptide residues present in the naturally occurring product is replaced, or in which the N- or C-terminal is modified.

Preferred calcitonins for use in accordance with the invention are salmon, human and porcine calcitonins and Elcatonin. All of these compounds are commercially available and have been extensively described, together with their pharmaceutical properties, in the literature.

As previously indicated it has been found that exceptionally good results, e.g. in terms of bio-availability levels and duration of presence in the blood plasma, are obtained on nasal administration of salmon calcitonin. Salmon calcitonin is accordingly the most preferred calcitonin for use in accordance with the invention.

As will be appreciated the calcitonins for use in the invention may be in free form or in pharmaceutically acceptable salt or complex form, e.g. in pharmaceutically acceptable acid addition salt form. Such salts and complexes are known and possess an equivalent degree of activity and tolerability to the free forms. Suitable acid addition salt forms for use in accordance with the invention include e.g. the hydrochlorides and acetates.

Benzalkonium chloride is the name commonly employed for known mixtures of quaternary ammonium salts typically of the generalized formula $C_6H_5-CH_2-NR(CH_3)_2Cl$, wherein R is C_8H_{17} to $C_{18}H_{37}$. A preferred concentration for the benzalkonium chloride component in the compositions of the invention is from about 0.002 to about 0.02, typically about 0.01% (w/v) of the total composition.

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The above defined compositions may be applied in accordance with the invention to the nasal mucosa e.g. either in drop or in spray form. As hereinafter described however, they are most preferably applied in spray form, i.e. in the form of finely divided droplets.

The composition of the invention may of course also include additional ingredients, in particular components belonging to the class of conventional pharmaceutically applicable surfactants. In this connection it has in accordance with a further aspect of the present invention been found that the use of surface active agents generally in relation to the nasal application of calcitonins, in particular salmon calcitonin, may increase resorption via the nasal mucosa and hence improve obtained bio-availability rates. Accordingly in a further aspect the present invention also provides a composition adapted for administration in the form of a liquid nasal spray, comprising:

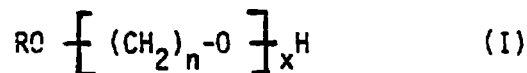
- i) a calcitonin, and
- iv) a surfactant suitable for application to the nasal mucosa, in
- iii) a liquid diluent or carrier suitable for application to the nasal mucosa.

Preferably the liquid diluent or carrier (iii) for use in the compositions of the invention [i.e., whether comprising ii) benzalkonium chloride and/or iv) a conventional surfactant as a necessary component] will comprise water (pharmaceutical grade). Most preferably it comprises aqueous saline. The compositions of the invention are formulated so as to permit administration via the nasal route. For this purpose they may also contain, e.g. minimum amounts of any additional ingredients or excipients desired, for example, additional preservatives or e.g. ciliary stimulants such as caffeine. Generally for nasal administration a mildly

acid pH will be preferred. Preferably the composition of the invention have a pH of from 3 to 5, most preferably from 3.5 to 4.5. Adjustment of the pH is achieved by addition of an appropriate acid, such as hydrochloric acid.

- 5 The compositions of the invention should also possess an appropriate isotonicity and viscosity. Preferably they have an osmotic pressure of from 260 to 380 mOsm/litre. Desired viscosity for the compositions of the invention will depend on the particular form for administration, e.g. whether administration
- 10 is to be by nasal drops or nasal spray. For nasal drops an appropriate viscosity is from 2 to 40×10^{-3} Pa.S.. For nasal sprays the viscosity will suitably be less than 2×10^{-3} Pa.S., e.g. from 1 to 2×10^{-3} Pa.S.

- Where compositions in accordance with the invention comprise
- 15 a conventional surfactant (whether or not they also comprise benzalkonium chloride) non-ionic surfactants are preferred. Especially preferred surfactants are polyoxyalkylene higher alcohol ethers, (higher means C12 to C16) e.g. of the general formula (I)



- 20 wherein RO is the residue of a higher alcohol especially a higher alkanol or alkylphenol, such as lauryl or cetyl alcohol, or a sterol residue, especially a lanosterol, dihydrocholesterol or cholesterol residue, as well as mixtures of two or more such ethers. Preferred polyoxyalkylene ethers for use in accordance with the
- 25 invention are polyoxyethylene and polyoxypropylene ethers (i.e. wherein n in the formula above is 2 or 3) in particular polyoxyethylene and polyoxyethylene lauryl, cetyl and cholesteryl ethers as well as mixtures of two or more such ethers.

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The hydroxy group at the end alkylene unit of such ethers as aforesaid may be partially or completely acylated, by e.g. acyl residues of aliphatic carboxylic acids, such as acetic acid.

5 Preferred ethers for use in accordance with the invention have a hydrophilic-lipophilic balance (HLB group number) of from about 10 to about 20, especially from about 12 to about 16.

10 Especially suitable ethers for use in accordance with the invention are those wherein the average number of repeating units in the polyoxyalkylene moiety (x in the formula above) is from 4 to 75, suitably 8 to 30, more especially 16 to 26. The ethers may be obtained in accordance with known techniques. A wide variety of such products are commercially available and e.g. offered for sale e.g. by the company Amerchol under the trade-name Solulan[®],
15 the companies KAO Soap, ICI and Atlas under the trade-names Emalex[®], Brij[®] and Laureth[®] and from the company Croda under the trade-name Cetomacrogol[®].

20 Examples of polyoxyalkylene ethers suitable for use in accordance with the invention are as follows:
(POE = polyoxyethylene ether; POP = polyoxypropylene ether; x = average No. of repeating units in the POP/POE moiety).

1. Cholesteryl ethers:

1.1 Solulan[®] C-24 - POE, x = 24.

2. Ethers of Lanolin alcohols:

2.1 Solulan[®] 16 - POE, x = 16.

25 2.2 Solulan[®] 25 - POE, x = 25.

2.3 Solulan[®] 75 - POE, x = 75.

- 2.4 Solulan[®] PB-10 - PPE, x = 10.
- 2.5 Solulan[®] 98 - POE, x = 10 - partially acetylated.
- 2.6 Solulan[®] 97 - POE, x = 9 - fully acetylated.

3. Lauryl ethers:

- 5 3.1 Emalex[®] 709 / Laureth[®] 9 - POE, x = 9.
- 3.2 Laureth[®] 4 / Brij[®] 30 - POE, x = 4.
- 3.3 Laureth[®] 23 / Brij[®] 35 - POE, x = 23.

4. Cetyl ethers:

- 4.1 Cetomacrogol[®] - POE, x = 20 to 24.

10 Lanolin alcohols are also known as wool fat alcohols and are a mixture of cholesterol, dihydrocholesterol and lanosterol.

15 Preferred esters for use in accordance with the present invention are polyoxyethylene cholesteryl ethers, i.e. of the above formula I, wherein n = 2 and R0 is a cholesterol residue, especially such ethers wherein the number of repeating units in the polyoxyethylene moiety is from 16 to 26, most preferably about 24.

20 More preferably such ethers are substantially free from contaminants in particular from other polyoxyalkylene ethers. Most preferably they comprise at least 75%, more preferably at least 85%, and most preferably at least 90% by weight of pure polyoxyethylene cholesteryl ether.

25 When a surfactant, e.g. a polyoxyalkylene ether is employed, the amount present in the compositions of the invention will vary depending on the particular surfactant chosen, the particular mode of administration (e.g. drop or spray) and the effect desired.

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In general, however, the amount present will be of the order of from . . . 2.0 to . . . 200 (preferably to . . . 100, more preferably to . . . 20), suitably from . . . 5 to . . . 30 (preferably to . . . 15), and most preferably about 10 mg/ml.

5 The amount of calcitonin to be administered in accordance with the method of the invention and hence the amount of active ingredient in the composition of the invention will, of course, depend on the particular calcitonin chosen, the condition to be treated, the desired frequency of administration and the effect
10 desired.

As indicated in the following example 2, bio-availability for calcitonins, in particular salmon calcitonin, as determined in terms of blood-plasma concentration following nasal administration in accordance with the teachings of the present invention has
15 been found to be surprisingly high, generally of the order of ca. 50% of levels achieved on intra-muscular injection. Accordingly administration in accordance with the invention will appropriately be effected so as to give a dosage rate of the order of 2x or more, e.g. from about 2 to 4x the dosage rate required for treatment
20 via intra-parietal, e.g. intra-muscular, administration.

Hitherto, where calcitonin, e.g. salmon calcitonin, treatment has been effected by intra-muscular injection, individual dosages of ca. 50 to 100 MRC units are applied at a rate of from ca. 1x daily to ca. 3x weekly. For nasal administration in accordance
25 with the present invention, treatment will therefore suitably comprise administration of dosages of from about 50 to about 400 MRC units, more preferably from about 100 to about 200 MRC units at a frequency of from about 1x daily to about 3x weekly. Conveniently dosages as aforesaid will be administered in a single application,
30 i.e. treatment will comprise administration of single nasal dosages

comprising about 50 to about 400 MRC units, preferably about 100 to about 200 MRC units, calcitonin. Alternatively such dosages may be split over a series of e.g. 2 to 4 applications taken at intervals during the day, the dosage at each application then
5 comprising about 10 to about 200, preferably about 25 to about 100 MRC units.

The total composition quantity administered at each nasal application suitably comprises from 0.05 to 0.15 ml, typically 0.1 ml e.g. 0.09 ml. Compositions for use in accordance
10 with the invention accordingly suitably comprise from 100, e.g. 150 to 8,000, preferably from 500 to 4,000, more preferably from 500 to 2,500, and most preferably from 1,000 to 2,000 MRC units calcitonin, e.g. salmon calcitonin, per ml.

15 For the purposes of nasal administration, the compositions of the invention will preferably be put up in a container provided with means enabling application of the contained composition to the nasal mucosa, e.g. put up in a nasal applicator device. Suitable applicators are known in the art and include those adapted for
20 administration of liquid compositions to the nasal mucosa in drop or spray form. Since dosaging with calcitonins should be as accurately controlled as possible use of spray applicators for which the administered quantity is susceptible to precise regulation will generally be preferred. Suitable administrators include e.g. atomising
25 devices, e.g. pump-atomizers and aerosol dispensers. In the latter case, the applicator will contain composition in accordance with the invention together with a propellant medium suitable for use in a nasal applicator. The atomising device will be provided with an appropriate spray adaptor allowing delivery of the contained
30 composition to the nasal mucosa. Such devices are well known in the art.

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The container, e.g. nasal applicator, may contain sufficient composition for a single nasal dosaging or for the supply of several sequential dosages, e.g. over a period of days or weeks. Quantities of individual dosages supplied will preferably be as hereinbefore defined.

In accordance with the foregoing the present invention further provides:

A. A container containing a pharmaceutical composition for nasal administration comprising

- 10 i) a calcitonin, and
 ii) benzalkonium chloride, in
 iii) a liquid diluent or carrier, suitable for application to the nasal mucosa,

15 said container being provided with means enabling application of the contained composition to the nasal mucosa, preferably in spray form;

B. An applicator device containing a pharmaceutical composition and provided with means enabling application of the contained composition to the nasal mucosa in spray form, said contained composition comprising

- 20 i) calcitonin, and
 iv) a surfactant suitable for application to the nasal mucosa, in
 iii) a liquid diluent or carrier suitable for application to the nasal mucosa;

25

as well as

A method of administering a calcitonin to a subject requiring calcitonin treatment, . . . comprises administering a composition for nasal administration comprising components

i), ii) and iii) as defined under A above, or comprising components i), iv) and iii) as defined under B above, to said subject via the nasal route.

5 Containers/applicator devices as defined under A and B above are suitably nasal aerosol applicators. Preferably they enable application of the contained composition in individual fixed quantities of from 0.05 to 0.15 ml, e.g. about 0.1 ml.

10 Suitable composition as well as individual components (i), (ii), (iii) or (iv) for use in relation to the containers/applicator devices/methods defined under A, B and C above are as hereinbefore described. Suitable dosaging regimens for use in relation to the method C of the invention are also as hereinbefore described.

15 In addition to the foregoing the present invention also provides a method for the production of a liquid pharmaceutical composition for nasal administration comprising

- 20
- i) a calcitonin, and
 - ii) benzalkonium chloride, and/or
 - iv) a surfactant suitable for application to the nasal mucosa, in
 - iii) a liquid diluent or carrier suitable for application to the nasal mucosa,

25 which method comprises bringing component (i) together with component (ii) and/or component (iv) into intimate admixture, e.g. into solution in component iii), and when required introducing the obtained composition into a container provided with means enabling application of the said obtained composition to the nasal mucosa, suitably enabling application of the said obtained composition

30 to the nasal mucosa in spray form.

The stability of the compositions of the invention may be determined in conventional manner.

The calcitonin content of the compositions of the invention under an inert nitrogen atmosphere will degrade less than 10% in 2 years at 20°C as indicated by standard analytical tests.

For example the nasal spray composition of Example 1 hereinafter described was stored for 2 months at 5°C, 20°C and 30°C under nitrogen in a glass container. No detectable (less than 1%) degradation of calcitonin was observed at 5°C and 20°C. At 30°C a 4% degradation was observed this being no more than expected for a pure aqueous solution. These results indicate adequate stability, i.e. less than 10% degradation over 2 years under nitrogen in a sealed container.

Also the compositions of the invention containing benzalkonium chloride are stable towards contamination by germs, e.g. according to standard tests, e.g. according to the procedures set out in S. Urban et al, Zbl. Bakt. Hyg. I Abt. Orig.B. 1972, 478-484 (1981) and S. Urban, Acta Pharm. Technol. 22, 247-253 (1976). For example the cell count of standard bacteria, namely E. coli ATCC 8739, Pseud. aeruginosa ATCC 9027, Staph. aureus ATCC 6538, Strept. pyogenes ATCC 8668, and standard fungi Cand. albicans ATCC 10231, Sacch. cerevisiae ATCC 9763, Aspergillus niger ATCC 16404 and Pen. steckii ATCC 10499 following inoculation of the composition will be reduced to 0.1% or less within 24 hours as indicated by standard tests.

In one stability test the nasal spray composition of Example 1 hereinafter was stored at 30°C for 3 months under a nitrogen atmosphere in a glass container. Pseud. aeruginosa ATCC 9027, Staph. aureus ATCC 6538, Strept. pyogenes ATCC 8668 and the fungi Cand. Albicans ATCC 10231, Sacch. cerevisiae ATCC 9763, Aspergillus niger ATCC 16404 and Pen. steckii ATCC 10499 were added to give

a cell count of ca. 2×10^5 organisms in the inoculated liquid. Within 2 hours the cell count had decreased to less than 0.1%. Within 4 weeks no cells could be detected.

5 Moreover the compositions are well tolerated as indicated in standard tests, e.g. in that less than 50% inhibition of ciliary beating frequency is observed up to 20 minutes after administration, according to the microphoto-oscillographic method of L. Chevance et al, Acta Otolaryng. 70, 26-28 (1970).

10 Insignificant or no prickling sensation and a good stability against contamination during use, may also be demonstrated in standard clinical testing.

Except where otherwise clear percentages used herein are weight by weight.

The following examples illustrate the invention.

EXAMPLE 1

COMPOSITION CONTAINING SALMON CALCITONIN SUITABLE FOR NASAL
ADMINISTRATION:

	<u>Ingredient</u>	<u>Quantity (per ml)</u>
5	1) Salmon calcitonin (active ingredient)	0.1375 mg
	10% excess	<u>0.01375 mg</u>
		0.15125 mg
	2) NaCl	7.5 mg
	3) Benzalkonium chloride	0.1 mg
10	4) HCl (1 N)	added to pH 3.7
	5) Distilled water	to an end volume of 1.0 ml.

Components 1 to 3 are combined under protection of nitrogen gas (on a scale to produce a final volume of 2500 ml) in conventional manner, with 10% of salmon calcitonin being added to allow for loss at filtration. 4) is then added to bring the pH to 3.7 and distilled water added to an end-volume of 2500 ml. The obtained solution is filtered (e.g. using a 0.2 μ m filter) to give a composition suitable for nasal application and for filling into a spray nasal dispenser with a solution volume of 2 ml. The composition comprises ca. 550 MRC-units active ingredient/ml, and the applicator delivers a quantity comprising 55 units per actuation.

EXAMPLE 2

RELATIVE BIO-AVAILABILITY STUDY: NASAL ADMINISTRATION/INTRA-MUSCULAR
INJECTION OF SALMON CALCITONIN

5 The study is conducted with 12 healthy volunteers, 6 male and
6 female, with a body weight of from 50 to 85 kg. Each subject
receives 4 administrations of salmon calcitonin, one intra-muscularly
and 3 nasally. Administration is effected at the following dosages:

10 A. Nasal: A1. 55 MRC units.
A2. 110 MRC units.
A3. 220 MRC units.

B. Intra-muscular: 50 MRC units.

15 Nasal administration is effected using composition in accordance
with example 1 and a spray-applicator delivering 55 MRC units
per individual spray dosage. For the purposes of administration
the subject is laid on the back with the head tilted backwards
for 5 minutes. The nostrils are cleaned by blowing of the nose
immediately prior to administration.

20 Intra-muscular administration is effected by injection of a single
1 ml dose of a composition similar to that of example 1, but omitting
benzalkonium chloride and containing 50 MRC units into the gluteus
medius muscle.

25 Each subject receives the 4 administrations in randomised sequence,
and at least 3 days are allowed between consecutive administrations.
Each administration is effected in the morning after a light break-
fast from which milk, butter and cheese is excluded. 100 ml water
or orange juice is taken hourly following treatment to maintain

urinary output. Further food is allowed not earlier than 4 hours after treatment.

Blood samples are taken immediately prior to administration (control), and at intervals of 5, 15, 30, 60, 90, 120, 180, 240, 360 and 480 minutes following administration. For the control a 20 ml sample is taken. All subsequent samples are 2 ml samples.

The concentration of salmon calcitonin in each serum sample is measured by radio-immuno-assay. Blood-pressure is controlled during the course of the trial and urine-samples tested for possible adverse reaction. Occurrence of side-effects, e.g. symptoms of nausea, is noted.

The AUC ("area under curve") for salmon calcitonin plasma concentration is calculated statistically, once employing all value, including those below the 26 pg/ml detectability limit, once with values below the detectability limit read as zero. Maximal plasma concentration and time at which this is reached are also determined. Relative bio-availability for nasal administration is determined from the relative dosage-standardized AUC (i.e. based on 50 MRC units) following nasal and intra-muscular administration.

Results obtained indicate that AUC values following administration of both 110 and 220 MRC units intra-nasally, are comparable with AUC values obtained following administration of 50 MRC units i.m., with serum levels for salmon calcitonin remaining above the detectability limit for 8 hours following nasal application of 110 MRC units as compared with 6 hours following i.m. application of 50 MRC units. No adverse side-effects were recorded following nasal administrations, even at the highest dosage of 220 MRC units.

EXAMPLE 3

COMPOSITIONS CONTAINING SALMON CALCITONIN SUITABLE FOR NASAL
ADMINISTRATION

<u>Composition No.</u>	<u>Quantity of salmon calcitonin employed</u>
5	
3a	0.06875 mg/ml
3b	0.275 mg/ml
3c	0.55 mg/ml
3d	1.1 mg/ml
10	The compositions are prepared analogously to example 1 employing the same quantities of components 2) and 3) (7.5 mg or 0.1 mg/ml respectively), identical adjustment to pH 3.7 employing component 4) and topping up to the required end-volume employing component 5). The obtained composition comprise ca. 250 (composition 3a),
15	
20	

EXAMPLE 4

COMPOSITIONS CONTAINING SALMON CALCITONIN TOGETHER WITH A
NON-IONIC SURFACTANT SUITABLE FOR NASAL ADMINISTRATION

The compositions are prepared in analogous manner to example 1 but with the addition of the following ingredients:

<u>Composition</u>	<u>Additional Ingredient</u>	<u>Quantity</u>
4a	polyoxyethylene cholesteryl ether: x = 24	30 mg/ml
4b	polyoxyethylene cholesteryl ether: x = 24	10 mg/ml
4c	polyoxyethylene cetyl ether: x = 20 to 24	100 mg/ml

- 5 The compositions are put up in a nasal applicator as described in Example 1.

EXAMPLE 5

COMPARATIVE BIO-AVAILABILITY STUDY FOR THE COMPOSITIONS OF EXAMPLES 1 AND 4a

- 10 0.2 ml portions of composition 1 or 4a were administered nasally by means of a nasal spray applicator to Rhesus monkeys (0.1 ml/nos-
tril) giving a dosage rate of ca. 100 MRC units salmon calcitonin/mon-
key, and salmon calcitonin plasma levels were measured in the
subsequent 6 hours. 3 runs were conducted per composition, and
15 the combined results plotted graphically. Results (c.f. graph
following) indicate that the bio-availability for both compositions
(area under curve) is substantially equivalent, with the peak
maximum being achieved somewhat earlier in the case of the composition
of Example 4a.

CLAIMS

1. A liquid nasal pharmaceutical composition for nasal administration comprising:
 - i) a calcitonin, and
 - 5 ii) benzalkonium chloride, in
 - iii) a liquid diluent or carrier, suitable for application to the nasal mucosa.
2. A composition according to claim 1, wherein ii) is present in a concentration of from 0.002 to 0.02% (w/v).
- 10 3. A composition according to claim 1 or 2 additionally comprising iv) a surfactant suitable for application to the nasal mucosa.
4. A composition according to any one of the preceding claims adapted for administration in the form of a nasal spray.
- 15 5. A liquid nasal pharmaceutical composition adapted for administration in the form of a liquid nasal spray, comprising:
 - i) a calcitonin, and
 - iv) a surfactant suitable for application to the nasal mucosa, in
 - iii) a liquid diluent or carrier suitable for application
 - 20 to the nasal mucosa.
6. A composition according to any one of the preceding claims, wherein i) is salmon calcitonin, human calcitonin, porcine calcitonin or elcatonin.





7. A composition according to any one of the preceding claims, wherein iii) comprises water.
8. A composition according to claim 7, wherein iii) comprises aqueous saline.
- 5 9. A composition according to any one of the preceding claims, wherein i) is present in an amount of from 100 to 8,000 MRC units/ml.
10. A composition according to claim 9, wherein i) is present in an amount of from 500 to 4,000 MRC units/ml.
- 10 11. A composition according to claim 10, wherein i) is present in an amount of from 500 to 2,500 MRC units/ml.
12. A composition according to claim 11, wherein i) is present in an amount of from 1,000 to 2,000 MRC units/ml.
13. A composition according to any one of claims 9 to 12 wherein i) is salmon calcitonin.
- 15 14. A composition according to claim 3 or 5, wherein iv) is a non-ionic surfactant.
15. A composition according to claim 14, wherein iv) comprises a polyoxyalkylene lauryl ether.
- 20 16. A composition according to claim 15, wherein iv) comprises a polyoxyalkylene cetyl ether.
17. A composition according to claim 15 or 16, wherein iv) comprises a polyoxyalkylene lanosteryl ether.



18. A composition according to claim 17, wherein iv) comprises
a polyoxyalkylene dihydrocholesteryl
ether.
19. A composition according to claim 18, wherein iv) comprises
5 a polyoxyethylene cholesteryl ether.
20. A composition according to claim 19, wherein iv) comprises
a polyoxyethylene cholesteryl ether in which the number of
repeating units in the polyoxyethylene moiety is from 16
to 26.
- 10 21. A composition according to any one of claims 3, 5 or 14 to
20 wherein iv) is present in an amount of from 2.0
to 200 mg/ml.
22. A composition according to claim 21 wherein iv) is present
in an amount of from 5 to 15 mg/ml.
- 15 23. A composition according to any one of the preceding claims
having a pH of from 3 to 5.
24. A composition according to claim 23 having a pH of from
3.5 to 4.5.
- 20 25. A composition according to claim 23 or 24 comprising hydrochloric
acid as the means to obtain the desired pH.
26. A composition according to any one of the preceding claims
having an osmotic pressure of from 260 to 380 mOsm/litre.
27. A composition according to any one of the preceding claims
for administration in the form of a spray and having a viscosity
25 of less than 2×10^{-3} Pa.S.



23

24

28. A container containing a composition as claimed in any one of claims 1 to 4 or 6 to 27 and provided with means enabling application of the contained composition to the nasal mucosa.
- 5 29. A container according to claim 28 provided with means enabling application of the contained composition to the nasal mucosa in spray form.
30. A container according to claim 29 which is a nasal aerosol applicator.
- 10 31. An applicator device containing a pharmaceutical composition and provided with means enabling application of the contained composition to the nasal mucosa in spray form, said contained composition comprising:
- 15 i) a calcitonin, and
 iv) a surfactant suitable for application to the nasal mucosa, in
 iii) a liquid diluent or carrier suitable for application to the nasal mucosa.
- 20 32. An applicator device as claimed in claim 31 wherein, in the contained composition, components i), iv) and iii) are as defined or are present in an amount as specified in any one of claims 6 to 22, or wherein the contained composition comprises an additional component or possesses physical characteristics as defined in any one of claims 23 to 27.



* C L M S *

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33. Use of benzalkonium chloride or a surfactant in the production of a liquid pharmaceutical composition as defined in any one of claims 1 to 27 suitable for nasal administration.
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