

(CONVENTION. By one or more persons and/or a Comp



COMMONWEALTH OF AUSTRALIA

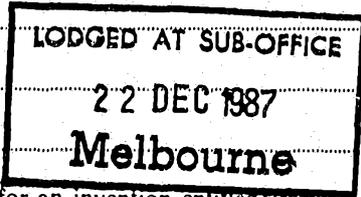
Patents Act 1952-1961

CONVENTION APPLICATION FOR A PATENT

608268

(1) Here insert (in full) Name or Names of Applicant or Applicants, followed by Address (es).

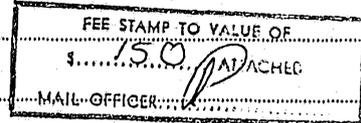
~~XX~~ (1) CIBA-GEIGY AG
We of Klybeckstrasse 141, 4002 Basle, Switzerland



(2) Here insert Title of Invention.

hereby apply for the grant of a Patent for an invention entitled:

NASAL SOLUTIONS



(3) Here insert number(s) of basic application(s)

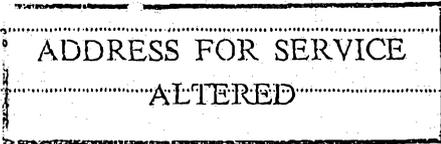
which is described in the accompanying complete specification. This application is a Convention application and is based on the application numbered (a)

5200./86-3

(4) Here insert Name of basic Country or Countries, and basic date or dates

for a patent or similar protection made in (4) Switzerland

on 23rd December 1986



APPLICATION ACCEPTED AND AMENDMENTS

ALLOWED

~~XX~~ Our address for service is Messrs. Arthur S. Cave & Co, Sydney
~~Edwd. Waters & Sons, Patent Attorneys,~~
50 Queen Street, Melbourne, Victoria, Australia.



DATED this 21st day of December 1987

(5) Signature (s) of Applicant (s) or Seal of Company and Signatures of its Officers as prescribed by its Articles of Association.

(5)

CIBA-GEIGY AG

by *[Signature]*

Ian A. Scott

Registered Patent Attorney

To:

4-16255/-

COMMONWEALTH OF AUSTRALIAPatents Act 1952 - 1969

DECLARATION IN SUPPORT OF A CONVENTION APPLICATION FOR A PATENT

In support of the Convention Application made by CIBA-GEIGY AG for a patent for an invention entitled:

Nasal solutions

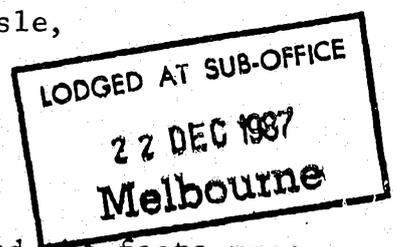
We, Arnold Seiler and) of CIBA-GEIGY AG, Klybeckstrasse 141,
Ernst Altherr) 4002 Basle, Switzerland
do solemnly and sincerely declare as follows:

1. We are authorised by the applicant for the patent to make this declaration on its behalf.
2. The basic application(s) as defined by Section 141 on the Act was(were) made in Switzerland on December 23, 1986

by CIBA-GEIGY AG, 4002 Basle, Switzerland

3. Leo Geller, Rudolf Wackernagel-Strasse 14, 4125 Riehen, Switzerland

Peter Glanzmann, J.J. Balmerstrasse 7, 4053 Basle, Switzerland



is(are) the actual inventor(s) of the invention and the facts upon which the applicant is entitled to make the application are as follows: The said applicant is the assignee of the actual inventor(s).

4. The basic application(s) referred to in paragraph 2 of this Declaration was(were) the first application(s) made in a Convention country in respect of the invention the subject of the application.

DECLARED at Basle, Switzerland on November 13, 1987

CIBA-GEIGY AG

To: The Commissioner of Patents

(12) PATENT ABRIDGMENT (11) Document No. AU-B-82955/87
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 608268

(54) Title
HUMAN CALCITONIN NASAL SOLUTIONS

international Patent Classification(s)
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(71) Applicant(s)
CIBA-GEIGY AG

(72) Inventor(s)
LEO GELLER; PETER GLANZMANN

(74) Attorney or Agent
ARTHUR S CAVE & CO, GPO Box 3876, SYDNEY NSW 2001

(56) Prior Art Documents
GB 2142335
FR 2312260
EP 115627

(57) Claim

1. A pharmaceutical solution for nasal administration comprising

a) a therapeutically effective amount of synthetic human calcitonin,

b) a viscosity-enhancing swellable polymer and

c) an aqueous carrier liquid containing optional isotonic components and/or additional excipients,

obtainable by mixing lyophilised synthetic human calcitonin, a viscosity-enhancing swellable polymer and an aqueous vehicle which contains optional isotonic components and/or additional excipients, in any order, simultaneously or in succession.

5. A method for the treatment of hypercalcaemic diseases in a human body which comprises administering to said body requiring said treatment an effective amount of the pharmaceutical composition defined in claim 1.

COMPLETE SPECIFICATION

(ORIGINAL)

608268

Class

Int. Class

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Complete Specification Lodged:
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Related Art:

This document contains the
amendments made under
Section 49 and is correct for
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Name of Applicant: CIBA-GEIGY AG

Address of Applicant: Klybeckstrasse 141, 4002 Basle, Switzerland

Actual Inventor: LEO GELLER and PETER GLANZMANN

Address for Service: ~~EDWD. WATERS & SONS;~~
~~50-QUEEN-STREET, MELBOURNE, AUSTRALIA, 3000.~~
Arthur S Cave & Co, Sydney



Complete Specification for the invention entitled:

NASAL SOLUTIONS

The following statement is a full description of this invention, including the best method of performing it known to us

4-16255/-

Nasal solutions

The present invention relates to pharmaceutical compositions in the form of aqueous solutions for administering human calcitonin, to the preparation of said pharmaceutical compositions, and to the use thereof.

5 Calcitonins belong to the group of biologically active parathyroid hormones and their structures are long polypeptide chains of varying activity. Certain calcitonins, e.g. human, salmon and eel calcitonin, can be prepared synthetically, are commercially available, and are widely used for the treatment of various diseases, for example Paget's disease, hypercalcemia or osteoporosis.

10 Dosage forms for the enteral administration of calcitonins, as also for other polypeptides such as insulin, pose problems. For example, calcitonins are rapidly degraded and are absorbed only slowly by body fluids. For this reason only dosage forms for parenteral administration have been used for such drugs. These dosage forms also have their problematical aspects, especially when administered intramuscularly or intravenously, as their suitability for self-medication is only limited and they can be painful. There is consequently a need for more convenient dosage forms which provide
15 the patient with an easily manageable form of self-medication with a bioavailability of the drug that permits effective therapy.

20 Nasal preparations, e.g. drops and sprays, for the administration of calcitonin are disclosed in German Offenlegungsschrift 3 335 086. The drawback of drops and sprays for nasal administration is, however, that these fluids flow out of nasal cavities too quickly.
25

5 In US patent specification 4 294 829 the proposal is made to administer calcitonin to the nose in the form of a powdery composition which contains methyl cellulose, instead of using drops or sprays. However, the administration of powders to the nose is normally unsuitable because of the irritation caused to dry mucous membranes. Moreover, doses cannot well be controlled when administering powders to the nasal cavity, for example with a spray applicator.

10 Published Japanese patent publication Sho-61-126014 discloses viscous aqueous solutions of calcitonin, e.g. salmon calcitonin, which contain hydroxypropyl cellulose as swellable polymer. When using human calcitonin, the solutions obtained by adding calcitonin to a solution of hydroxypropyl cellulose are not satisfactory. In Helvetica Chimica Acta, Vol. 53, Fasc. 8 (1980), No. 225, pp. 2135-2150, especially pp. 2141-2142, P. Sieber et al. describe the formation of associates, in particular fibrillae, of human calcitonin in aqueous solution. Such associates diminish the absorption capacity of human calcitonin.

15 Surprisingly, it has now been found that the formation of fibrillae can be avoided by lyophilising human calcitonin and dissolving the lyophilised drug in aqueous solution, and that it is possible to prepare a pharmaceutical composition in the form of an aqueous solution for the nasal administration of calcitonin in readily dosable amounts. Said pharmaceutical composition comprises

- 25
- a) a therapeutically effective amount of lyophilised human calcitonin or a derivative thereof,
 - b) a viscosity-enhancing swellable polymer, and
 - c) an aqueous carrier liquid which contains optional isotonic components and/or further excipients.

The general terms employed throughout this specification have the following preferred meanings:

5 The term "lower" used to qualify organic radicals or groups, e.g. lower alkyl, lower alkoxy, lower alkanoyl and the like, indicates that such organic radicals or groups, unless otherwise defined, contain up to 7, preferably up to 4, carbon atoms inclusive.

10 The term "human calcitonin" is used in a broad sense in the context of this description and is intended to comprise not only natural human calcitonin as described in *Helv. Chim. Acta*, Vol 53, loc. cit., which can also be obtained synthetically, but also pharmaceutically acceptable derivatives and analogues thereof, e.g. those in which one or more of the amino acid groups occurring in the natural compounds are replaced or the N- or C-terminal group has been structurally modified.

15 Human calcitonin can exist in the free form or in the form of a pharmaceutically acceptable acid addition salt. Such salts are known and their activity and compatibility are comparable to those of the free forms. Typical suitable acid addition salts are the hydrochlorides or acetates.

20 Exemplary of viscosity-enhancing swellable polymers are hydrophilic, partially etherified cellulose derivatives as well as hydrophilic polyacrylates, polymethylacrylates, polyethylene glycols or polyvinyl alcohols or mixtures of these polymers.

25 Hydrophilic, partially etherified cellulose derivatives are e.g. lower alkyl ethers of cellulose having an average molar degree of substitution (MS) greater than 1 and less than 3 and an average degree of polymerisation of c. 100-5000.

The degree of substitution denotes the number of hydroxy groups replaced by alkoxy groups per glycol unit. The average molar degree of substitution (MS) is a mean value and indicates the number of lower alkoxy groups per glycol unit in the polymer.

The average degree of polymerisation (DP) is also a mean value and indicates the average number of glycol units in the cellulose polymer.

Typical examples of lower alkyl ethers of cellulose are cellulose derivatives which are substituted at the hydroxymethyl group (primary hydroxy group) of the glucose unit forming the cellulose chains, and optionally at the second and third secondary hydroxy group, by C₁-C₄alkyl groups, preferably methyl or ethyl, or by substituted C₁-C₄alkyl groups, e.g. 2-hydroxyethyl, 3-hydroxy-n-propyl, carboxymethyl or 2-carboxyethyl.

Suitable lower alkyl ethers of cellulose are preferably cellulose derivatives which are substituted at the hydroxymethyl group (primary hydroxy group) of the glucose unit by the cited C₁-C₄alkyl groups or by substituted C₁-C₄alkyl groups, and at the second and, optionally, third secondary hydroxyl group by methyl or ethyl groups.

Particularly suitable lower alkyl ethers of cellulose are methyl cellulose, ethyl cellulose, hydroxyethyl methyl cellulose, hydroxypropyl methyl cellulose, hydroxyethyl ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose (in salt form, e.g. as sodium salt), or carboxymethyl methyl cellulose (also in salt form, e.g. as sodium salt).

Preferred lower alkyl ethers of cellulose are: methyl cellulose (DP: c. 200-1000, MS: c. 1.4-2.0), hydroxyethyl cellulose (DP: c. 120-1200, MS: c. 1.2-2.5), hydroxypropyl cellulose (DP: c. 200-3000, MS: c. 1.0-3.0) and hydroxypropyl methyl cellulose (DP: c. 200-1000, MS: c. 1.4-2.0).

Hydrophilic polyacrylates which can be used as viscosity-enhancing swellable polymers have an average molecular weight of c. 8.6×10^5 to 1.0×10^6 . The polyacrylic acid chains may carry short side chains, whereby the individual commercial forms differ in addition to having different molecular weights. It is preferred to use polyacrylic acid derivatives which are neutralised, e.g. with dilute aqueous sodium hydroxide solution, and which are sold under the registered trademark Carbopol® (Goodrich), e.g. Carbopol 934 P or Carbopol 940.

Suitable polymethacrylates are also swellable and have an average molecular weight greater than 1.0×10^6 . Preferred suitable commercial forms are the polymers of methacrylic acid and methacrylates of the Eudragit® type, e.g. Eudragit L or Eudragit S (Röhm GmbH).

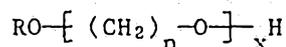
Suitable polyethylene glycols have an average molecular weight of c. 400 to 600. Commercial forms having pharmaceutical qualities are preferred, e.g. polyethylene glycol such as Lutrol® (BASF), Polydiol®, Polywachs® (Hüls), Polyglycol®, Lanogen® (Hoechst), Carbowax® (Union Carbide), Plurocol® (Wyandotte) or Tetronic® (Kuhlmann).

Suitable polyvinyl alcohols have an average molecular weight of c. 28,000 to 40,000 and the properties and qualities described in Hagers Handbuch der Pharmazeutischen Praxis (Hager's Handbook of Pharmaceutical Practice), Springer Verlag, Vol. VIIa, pp. 833-834, referred to hereinafter as "Hager".

The aqueous carrier liquid has a pH value below 6, which is reached after the defined amount of lyophilised calcitonin has dissolved in the requisite amount of liquid. In accordance with the nature and preparation of the active drug employed, the pH may be in the range from 3 to 6 after the active drug has dissolved in the aqueous vehicle.

The aqueous carrier liquid preferably contains isotonic components, e.g. ionic isotonic components such as sodium chloride, or nonionic isotonic components such as sorbitol, mannitol or glucose (builders), and in the usual concentration employed for preparing isotonic solutions and prescribed in Hager, Vol. VIIa, pp. 225-239. It is preferred to use calcium-free isotonic sodium chloride solution or sorbitol solution as aqueous vehicle.

The aqueous vehicle can also contain further pharmaceutically acceptable excipients, e.g. preservatives such as benzalkonium chloride, surfactants for improving the flow properties, preferably nonionic surfactants selected from the group of the polyoxyalkylene ethers of higher alcohols, e.g. of formula



wherein RO is the hydrophobic radical of a higher alcohol, e.g. lauryl or cetyl alcohol, of an alkyl phenol, or of a sterol, e.g. lanosterol, dihydrocholesterol or cholesterol, as well as mixtures of two or more such ethers. Preferred polyoxyalkylene ethers are polyoxyethylene and polyoxypropylene ethers carrying hydrophobic groups (i.e. wherein n in the above formula is 2 or 3), most preferably lauryl ether, cetyl ether and cholesterol polyoxyethylene and cholesterol polyoxypropylene ether, as well as mixtures of two or more such ethers.

The hydroxyl groups at the terminal radical of these above mentioned ethers can be partially or completely acylated, e.g. with acyl radicals of aliphatic carboxylic acids such as acetic acid.

Preferred polyethers have a hydrophilic-lipophilic ratio (HLB value) of c. 10 to 20, in particular from c. 12 to 16.

Particularly suitable polyethers have an average value of the recurring units in the polyoxyalkylene moiety (bracketed segment of the above formula) of from 4 to 75, preferably from 8 to 30 and,

most preferably, from 16 to 26. The polyethers can be obtained by known methods. A large selection of such products is commercially available and sold e.g. by Amerchol under the registered trademark Solulan[®], by Kao Soap, ICI and Atlas under the registered trademarks Emalex[®], Brij[®] and Laureth[®], and by Croda under the registered trademark Cetomacrogel[®].

Further particularly suitable surfactants are nonionic surfactants of the fatty acid polyhydroxy alcohol ester type such as sorbitan monolaurate, monooleate, monostearate or monopalmitate, sorbitan tristearate or trioleate, adducts of polyoxyethylene and fatty acid polyhydroxy alcohol esters such as polyoxyethylene sorbitan monolaurate, monooleate, monostearate, monopalmitate, tristearate or trioleate, polyethylene glycol fatty acid esters such as polyoxyethyl stearate, polyethylene glycol 400 stearate, polyethylene glycol 2000 stearate, in particular ethylene oxide/propylene oxide block polymers of the Pluronic[®] type (Wyandotte).

The aqueous carrier liquid can contain still further pharmaceutically acceptable excipients, e.g. essential oils for improving the aroma, e.g. menthol, paraffin or glycerol for improving the flow properties, sugar and/or sweeteners for improving the taste, fragrances and the like.

The nasal application of the pharmaceutical compositions permits a comfortable and simple self-administration of human calcitonin by the patient, so that the conventional parenteral administration by the attendant physician can be dispensed with.

The pharmaceutical compositions have good compatibility and long duration of action at the site of administration of the active drug. The high viscosity of the aqueous solution effects a prolonged retention time on the mucous membranes and thus an especially good absorption of the drug.

The aqueous solution for nasal application lowers the plasma calcium and plasma phosphate level in the blood of warm-blooded animals (man and animals) and can therefore be used for treating hypercalcemia and/or bone diseases such as Paget's disease or osteoporosis.

The dose of human calcitonin to be administered and the concentration of the drug in the pharmaceutical composition depend on the disease to be treated and on the condition of the patient.

The absorption of human calcitonin (which can be determined as blood plasma concentration) is surprisingly high after nasal administration. It can even reach values higher than those determined after intramuscular injection. The dose administered can be a multiple of the known doses conventionally used for intramuscular administration.

Up to now, individual doses of c. 5 mg of active drug have been administered about once daily to three times weekly when injecting human calcitonin subcutaneously or intramuscularly. Nasal administration in accordance with the practice of this invention will require, over the period of treatment, doses of c. 1.0 to 10.0 mg in a frequency of about once daily to three times weekly. The above doses can be administered in a single application, i.e. during treatment individual doses of 1.0 to 10.0 mg of calcitonin are administered to the nose. Alternatively, these amounts can also be administered in divided doses two to four times daily. The total volume of the composition for nasal administration is preferably c. 0.1 to 0.5 ml.

The present invention preferably relates to a pharmaceutical composition in the form of an aqueous solution for the nasal administration of synthetic human calcitonin, which solution has a viscosity range of about 20-300 mPa·s (at 25°C). Said pharmaceutical composition preferably comprises:

- a) a therapeutically effective amount of synthetic human calcitonin,
- b) c. 0.2 to 3.0 % by weight of methyl cellulose or hydroxypropyl methyl cellulose (DP: c. 200-1000, MS: c. 1.4-2.0), and
- c) an aqueous carrier liquid containing isotonic components.

The present invention relates most preferably to a pharmaceutical composition in the form of an aqueous solution for the nasal administration of synthetic human calcitonin, which solution has a viscosity range of about 20-100 mPa·s (at 25°C). Said pharmaceutical composition preferably comprises:

- a) a therapeutically effective amount of synthetic human calcitonin,
- b) c. 0.5 to 1.0 % by weight of methyl cellulose or hydroxypropyl methyl cellulose (DP: c. 200-1000, MS: c. 1.4-2.0), and
- c) an aqueous carrier liquid containing isotonic components.

The present invention also relates to a process for the preparation of a pharmaceutical composition in the form of an aqueous solution containing calcitonin, which comprises mixing

- a) a therapeutically effective amount of lyophilised human calcitonin or a derivative thereof,
- b) a viscosity-enhancing swellable polymer, and
- c) an aqueous carrier liquid which contains optional isotonic components and/or additional excipients,

in a manner known per se and in any order, simultaneously or in succession.

A preferred embodiment of the process comprises preparing lyophilised human calcitonin by e.g. dissolving the calcitonin with the requisite amount of nonionic isotonic component (builder), e.g. mannitol, in distilled water, adjusting the pH of the solution to c. 4-6 with a dilute aqueous sodium hydroxide solution, filtering the solution under sterile conditions and subsequently lyophilising the sterile solution. The lyophilised calcitonin is added to a solution (mucilage) containing the swellable polymer, e.g. hydroxypropyl methyl cellulose or methyl cellulose, and adding further optional isotonic components such as sorbitol and preservatives such as benzalkonium chloride, and dissolving them. The patient can then apply this viscous solution to the nose using a drop applicator.

The pharmaceutical compositions of the invention are preferably isotonic and the osmotic pressure can vary from 260 to 380 mOsm/kg.

The desired viscosity range can be adjusted by addition of suitable amounts of component b). If the viscosity is too low, the fluid flows out of the nasal cavity too quickly. If the viscosity is too high, the fluid becomes tacky and difficult to apply. Aqueous solutions containing c. 0.2-3 % of methyl cellulose or hydroxypropyl methyl cellulose (DP: c. 200-1000, MS: c. 1.4-2.0) have a particularly suitable viscosity range. The suitable viscosities at 20°C are in the order of magnitude of c. 5-5000 mPa·s, preferably 20-300 mPa·s and, most preferably, 20-100 mPa·s (25°C). Reference is made in this connection to the precise directions given in Hager, Vol. VII, pp. 115-118, wherein the preparation of aqueous solutions of the desired viscosity as a function of the concentration of the respective viscosity-enhancing swellable polymer is described. By addition of active drug, osmotic salts, surfactants and other adjuvants, the viscosity values of the pure solutions containing swellable polymers can vary. In general, the viscous solutions must have adequate flow properties and ensure sufficient moistening of the mucous membranes.

It is possible to administer the pharmaceutical compositions which contain the calcitonin a) and the swellable polymer b), together with excipients, in solution. This liquid dosage form can be administered to the patient by application to the nose in conventional manner by means of a drop applicator. The patient can self-administer the solution in the prescribed amount. The pharmaceutical compositions can also be prepared in situ, for example by adding lyophilised calcitonin, prior to use, to a previously prepared solution without the active drug but containing the swellable polymer and excipients, e.g. methyl cellulose or hydroxypropyl methyl cellulose and sorbitol or sodium chloride, and subsequently applying the mixture to the nose. The invention also relates to the use of the pharmaceutical compositions for the nasal administration of human calcitonin.

The following non-limitative Examples illustrate the field of use and operativeness of the invention.

Example 1:

a) Preparation of the lyophilised active drug

Components

CIBACALCIN®	10.0 mg
mannitol	10.0 mg

10 mg of CIBACALCIN (human calcitonin) and 10 mg of mannitol are dissolved at room temperature, under nitrogen, in 2.0 ml of distilled water. The pH is adjusted to 4.5 with c. 4 mg of 1N aqueous NaOH. The solution is filtered under sterile conditions through a membrane filter (0.2 μ m pore size) and the sterile solution is filled into a sterile glass vial. The vial is frozen at -40°C and lyophilised in a freeze-drying apparatus.

b) Preparation of the solution containing the swellable polymer

Components

Methocel® 90 HG 4000 cP	50.0 mg
sorbitol	500.0 mg
benzalkonium chloride	1.0 mg
dist. water	10.0 ml

Hydroxypropyl methyl cellulose (Methocel), sorbitol and benzalkonium chloride are mixed in distilled water. The mixture is allowed to swell for several hours at 5°C and the viscous solution is then filtered through a Scrynel® filter having a pore size of 10 microns. The filtered solution is filled into a glass vial and sterilised, e.g. in an autoclave. The pH of the sterilised solution is 6-7.

c) Preparation and application of the CIBACALCIN nasal solution (2.0 mg of lyophilised Cibacalcin/0.4 ml of swellable polymer solution)

1 vial containing the lyophilised active drug prepared in a) is dissolved in 2.0 ml of the solution prepared in b). The pH of the solution corresponds to that of the lyophilised drug. 0.4 ml of the viscous CIBACALCIN solution is applied with a drop applicator to the nose (both nostrils) of the recumbent patient.

Example 2:

a) In accordance with Example 1 a), lyophilised active drug formulations are prepared from 10 mg of Cibacalcin (without the addition of mannitol), 10 mg of Cibacalcin and 30 mg of mannitol, and 10 mg of Cibacalcin and 10 mg of mannitol and 2 mg of hydroxypropyl methyl cellulose (Methocel®). The pH of each solution to be lyophilised is adjusted to 3.5-6.0 with dilute aqueous sodium hydroxide solution.

b) As described in Example 1 b), solutions containing swellable polymer are prepared from 20 to 100 mg of hydroxypropyl methyl cellulose (Methocel), 500 mg of sorbitol and 1.0 mg of benzalkonium chloride, or from 20 to 100 mg of hydroxypropyl cellulose (Klucel®), 500 mg of sorbitol and 1.0 mg of benzalkonium chloride.

c) In accordance with the procedure of Example 1 c), the solutions prepared in b) are added to the lyophilised drug formulations prepared in a) and applied to the nose.



The Claims defining the invention are as follows:

1. A pharmaceutical solution for nasal administration comprising

- a) a therapeutically effective amount of synthetic human calcitonin,
- b) a viscosity-enhancing swellable polymer and
- c) an aqueous carrier liquid containing optional isotonic components and/or additional excipients,

obtainable by mixing lyophilised synthetic human calcitonin, a viscosity-enhancing swellable polymer and an aqueous vehicle which contains optional isotonic components and/or additional excipients, in any order, simultaneously or in succession.

2. A pharmaceutical composition according to claim 1 comprising

- a) a therapeutically effective amount of synthetic human calcitonin,
- b) 0.2 to 3 % by weight of methyl cellulose or hydroxypropyl methyl cellulose (DP: c. 200-1000, MS: c. 1.4-2.0), and
- c) an aqueous carrier liquid containing isotonic components.

3. A pharmaceutical composition according to claim 1 comprising

- a) a therapeutically effective amount of synthetic human calcitonin,
- b) 0.5 to 1.0 % by weight of methyl cellulose or hydroxypropyl methyl cellulose (DP: c. 200-1000, MS: c. 1.4-2.0), and
- c) an aqueous carrier liquid containing isotonic components.



4. A process for the preparation of a pharmaceutical composition according to claim 1, which comprises mixing

a) a therapeutically effective amount of lyophilized synthetic human calcitonin.

b) a viscosity-enhancing swellable polymer, and

c) an aqueous carrier liquid containing optional isotonic components and/or additional excipients,

in a manner known per se and in any order, simultaneously or in succession.

5. A method for the treatment of hypercalcaemic diseases in a human body which comprises administering to said body requiring said treatment an effective amount of the pharmaceutical composition defined in claim 1.

DATED this 18th day of December 1990

FO 7.4/RS/ms*

CIBA-GEIGY AG
By Its Agents
ARTHUR S. CAVE & CO.

