

Nasal Pharmaceutical Composition containing a
Somatostatin Analogue

The present invention relates to a novel means for the administration of the somatostatin analogue SMS 201-995 as well as to novel galenic compositions comprising this analogue.

Somatostatin or SRIF is a naturally occurring cyclic tetradecapeptide, first isolated from ovine and porcine hypothalamic tissue, having potent growth hormone (GH) inhibiting activity. It has since also been found to be present in other areas of the central nervous system as well as in the specialised D-cells of the pancreas, stomach and small intestine. From these locations SRIF acts on the pituitary to inhibit secretion of GH and thyroid stimulating hormone (TSH), on the pancreas to inhibit exocrine and endocrine secretion (including secretion of insulin and glucagon), and locally in the gastrointestinal (GI) tract where it inhibits release of gastrin secretion, CCK, VIP and possibly other hormones. Through the latter inhibiting effects SRIF plays an important physiological role in modulation gastro-intestinal function, e.g. by reducing gastric acid secretion, delaying stomach evacuation, slowing intestinal motility, decreasing bile flow, increasing mucous production and reducing splanchnic blood flow.

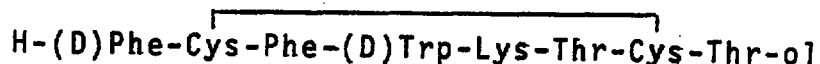
Various proposals have been made for the therapeutic application of this compound, e.g. in the treatment of acromegaly or gastrointestinal disorders such as gastro-intestinal bleeding. However, although biologically highly active, SRIF has a very short half life (2 to 3 minutes) and this, coupled with the

concomitant need for i.v. administration and the rebound phenomena observed at the end of i.v. administration, renders this substance unsuitable for long-term clinical use.

More recently therefore, research has concentrated on the development of novel analogues and derivatives of somatostatin-these being oligopeptide compounds comprising substantially fewer amino acid residues than somatostatin itself, but incorporating one or more partial peptide sequences occurring in the somatostatin molecule.

Hitherto all these analogues have to be administered by injection, e.g. i.v. or s.c. administration, in order to provide a therapeutically effect at non-toxic doses.

A particular analogue which shows especial therapeutic promise and is now in an advanced stage of clinical testing is the compound SMS 201-995 (hereinafter "SMS") of formula



The generic name for SMS is octreotide.

This compound which is specifically disclosed and claimed in European patent no. 0029579 (= USP 4,395,403), is an octapeptide possessing many of the same pharmacological properties as SRIF, though apparently somewhat more selective in inhibiting GH and glucagon rather than insulin release. Particular conditions for which use of this compound is proposed include treatment of acromegaly, diabetic complications and a variety of GI disorders including GI hormone secreting tumours (e.g. VIPomas and the like) .

For the purposes of therapeutic application SMS, like most other peptide drugs, may of course be administered as such, i.e. in free form, or in pharmaceutically acceptable salt and/or complex form. The SMS additionally or alternatively may be in solvate form, e.g. a hydrate.

The current form of choice for clinical application of SMS is the acetate hydrate referred to herein as SMSac, which has a free peptide content of ca. 80 to 88%, e.g. 83 to 87%. Unless otherwise indicated the terms "SMS" and "octreotide" as used throughout the present application and claims understood as designating both the free peptide and its pharmaceutically acceptable salts, in particular acid addition salts, especially the acetate, as well as pharmaceutically acceptable complexes and/or solvates thereof.

Though of very considerable therapeutic potential, practical difficulties are encountered in relation to administration of SMS; i.v. or s.c. administration has hitherto been the only route available permitting effective dosaging in clinic. Generally administration by injection or infusion is practiced. Such means of administration are always inconvenient and where long term therapy is required with administration at regular intervals, can cause considerable pain and inconvenience to the patient. The finding of alternative means of administration for SMS, in particular means which would permit ready self-application by the patient, e.g. for the purposes of out-patient treatment, has accordingly remained a major objective.

In accordance with the present invention it has now surprisingly been found that effective treatment with SMS can be obtained on nasal administration, i.e. via application to the nasal mucosae. In particular it has been found that on nasal admini-

stration at dosage levels which are well within the range of tolerability, bioavailability levels are achieved which are entirely adequate to permit effective long term treatment of conditions for which SMS therapy is to be employed, e.g. such as hereinbefore set forth.

Since the nasal route provides a simple and painless mode of administration, which may be repeated on a regular basis with no great inconvenience to the patient, the present invention accordingly meets previously existing needs as discussed above. The nasal compositions of the invention may be surprisingly very well tolerated, e.g. having a minimal effect on ciliary function.

In accordance with the foregoing the present invention provides:-

- i) A method of administering octreotide (SMS) to a subject requiring treatment therewith, e.g. for the purposes of treating disorders with an aetiology comprising or associated with excess GH secretion or of treating gastrointestinal disorders, for example as hereinbefore specified, which comprises administering octreotide (SMS) via the nasal route; as well as
- ii) A nasal pharmaceutical composition comprising octreotide (SMS), and
- iii) A process for the preparation of a nasal pharmaceutical composition which comprises working up octreotide (SMS) with nasal excipients.

The pharmaceutical composition may be formulated in conventional manner using excipients compatible with the nasal mucosae, e.g. as described hereinafter.

The pharmaceutical compositions may be formulated for local administration to the nasal mucous membrane, and capable of providing a systemic action of SMS. The formulation may be e.g. a liquid, an insert or a powder.

Compositions as defined under ii) above are for example liquid compositions comprising SMS together with a liquid diluent or carrier suitable for application to the nasal mucosae.

Such compositions are preferably adapted for administration in nasal spray or in drop form.

Appropriate liquid compositions ii) are in particular aqueous solutions. For the purposes of nasal application such solutions will preferably have a mildly acid pH e.g. of from about 4 to 5, preferably about 4.2. The required degree of acidity is conveniently achieved, e.g. by the addition of HCl or other appropriate mineral or organic acid. For the purposes of nasal administration such compositions will also preferably be isotonic or substantially isotonic. Preferred additives for achieving the desired degree of isotonicity include nasally acceptable sugars such as glucose, mannitol or sorbitol or nasally acceptable inorganic salts in particular NaCl. In accordance with the present invention the preferred additive for achieving the desired degree of isotonicity is glucose, ribose, mannose, arabinose, xylose or another aldose, or glucosamine.

The compositions of the present invention may also contain further ingredients or excipients known in the art for example stabilizing and/or preserving agents. Preferred preserving agents for use in the compositions of the invention are sodium methylmercurithiosalicylate (=Thiomersal) and benzalkonium chloride. Suitably any such preserving agent is present in an amount of from ca. 0.05 to 0.2 mg/ml e.g. ca. 0.1 mg/ml.

In another aspect the present invention provides a porous solid nasal insert having SMS dispersed therein. In yet another aspect the present invention provides a solid nasal insert comprising a porous matrix comprising gelatine and/or hydroxypropylmethylcellulose and SMS therein.

The nasal insert may be produced by any conventional method, e.g. by a) producing a distribution of SMS throughout a porous matrix comprising gelatine and/or hydroxypropylmethylcellulose, e.g. by lyophilising a liquid containing a polymer capable of forming a matrix, and SMS; or b) distributing a SMS throughout a nasal insert, for example by soaking a sponge in an aqueous solution at e.g. room temperature and evaporating off the solvent.

By the term "nasal insert" is to be understood, e.g. a device which is sized, shaped and adapted for placement and retention into the naris: intended for insertion into the naris; or which is formed, shaped or otherwise adapted for insertion into and/or retention in the naris; or which is shaped to substantially conform to the internal surface of the naris; or which is provided with means to facilitate insertion into and/or retention in the naris; or which is provided with a dispenser device to facilitate insertion into the naris; or which is provided together with instructions to effect insertion into the naris. The insert may be retained in the naris, but flushed by the nasal mucous, and may be designed to release the active agent at the same place in the naris. Suitable nasal insert types include nasal plugs, tampons and the like. Conveniently the volume and porosity of the insert are chosen such that it is retained in the naris, but breathing is not significantly inhibited. Suitable dimensions are e.g. from about 0.05 to about 1 cm³, e.g. about 0.5 to about 0.8 cm³. The shape may be approximately e.g. a cylinder, a cone, a cube or sphere.

The SMS may be carried on the insert, e.g. by adsorption onto the surface thereof, or in the insert, e.g. by absorption, or by any other convenient means, e.g. carried in combination with one or more nasally acceptable diluents or vehicles in the form of a coating, e.g. solid or semi-solid coating, upon the surface on the insert.

Alternatively, where the insert itself comprises a soluble or semi-soluble material, e.g. water-soluble polymers, or material otherwise degradable within the naris, for example a nasally acceptable proteinaceous material such as gelatin, the SMS may be present in solid form, e.g. in the form of

lyophilisate dispersed within the insert, e.g. distributed throughout the matrix.

Preferably SMS is carried, e.g. retained by absorption, in the insert and is suitably distributed throughout the insert.

Inserts in accordance with the invention are capable of releasing the peptide carried to the surface of the nasal mucosa. For this purpose they will preferably be so shaped or formed as to conform to the internal surface of the naris, e.g. so as to enable maximum contact between the surface of the insert and the nasal mucosa. Moreover, where the SMS is retained in the insert, e.g. by absorption, its characteristics e.g. the absorption characteristics of the material of which it is comprised, will suitably be such as to allow ready passage of the peptide to the surface of the insert following progressive uptake by the nasal mucosa from the insert surfaces.

Where agent is retained, e.g. by adsorption, in the insert, the insert may comprise any appropriate, e.g. nasally acceptable material, providing a porous matrix or reticulum in the interstices of which the peptide may be retained, e.g. absorbed. The material is conveniently elastic so it can be retained in the naris without discomfort. It may be for example, fibrous material, such as cotton wool or sponge material, such as natural or synthetic sponge.

If desired, the material may swell a little, e.g. increase in volume by about 50%, on administration.

The material from which the insert is made may be for example a water soluble polymer. Preferably the polymer is easily wettable by the nasal mucous. In the naris it may be biodegradable and, it may even dissolve slowly, e.g. over up to one or more days. It may have to be removed after the dose of active agent has been administered. An example is lyophilised absorbable gelatine sponge. If desired the matrix may dissolve by the time or shortly after the dose of active agent has been administered. Examples include water-soluble acrylate polymers and cellulose derivatives such as cellulose, e.g. hydroxypropylcellulose and especially hydroxypropylmethyl cellulose. Alternatively water-insoluble crystalline cellulose may be used.

The characteristics of the matrix material used, e.g. viscosity or molecular weight should be chosen such that these resultant insert is easy to handle and store. Typical molecular weights for hydroxypropyl methylcellulose are from about 9,000 to 15,000 and a viscosity e.g. 4 to around 15 cp, for a 2% solution.

Another suitable material is a gelatin sponge material. Specifications have been laid down in the US Pharmacopoeia for absorbable gelatine sponges, e.g. for hemostatis in surgical procedures and such sponges are preferred. Such sponges may be produced, e.g. by vigorously whipping an aqueous solution of pure gelatine to produce a foam, drying the foam under controlled conditions to give a sponge, cutting up the sponge and sterilizing the cut-up pieces. Suitable sizes are from about 5 x 5 x 5 to about 10 x 10 x 10 mm. The sponge is compressed by hand before use and is resorbed over a few hours. An especially suitable sponge material for use in the preparation of nasal inserts in accordance with the invention is the product SPONGOSTAN^R available from A/S Ferrosan, 5 Sydmarken, DK-2860 Soeborg, Denmark.

Alternative polymers are e.g. hydroxypropylcellulose or polyvinylpyrrolidone.

As indicated above the insert preferably has a porous structure. Conveniently the nasal mucous can wet the insert and the active agent may diffuse through the pores in the insert to the surface of the naris.

The pores of the insert may have a diameter of for example a few microns to about 100 microns. The pores of a lyophilised absorbable gelatin sponge may be for example from about 5 to 100 microns. The pore size may for example from about 5 to about 10 microns.

In sponge material the pores may be tortious. When the insert is produced under lyophilisation the pores may be approximately linear.

Preferably the insert contains a water-soluble sugar or like excipient to provide a stable structure to the insert. Examples of suitable sugars include lactose, saccharose, and mannitol. Preferably the weight ratio sugar to other material is from about 0.1 to 1 to about 10 to 1.

A preferred insert comprises a water-soluble polymer such as hydroxypropylmethyl cellulose and lactose. Under electron microscopy a lyophilised sample appears to comprise laminar sheets each having pores therein. The pores extend substantially throughout the sample.

Where the SMS is retained in the insert, e.g. by absorption, it will conveniently be carried in dilute form, e.g. in the form of a composition comprising the active agent together with a nasally acceptable fluid, e.g. liquid, diluent or vehicle therefor. Suitably such compositions will comprise the agent in the form of a solution, suspension, dispersion

or the like. Preferably such compositions will comprise the agent in aqueous solution.

The insert is preferably formed under substantially micro-organism-free or sterile conditions.

In one preferred variante a solution of the active agent is lyophilised. The insert may be preformed or formed during the lyophilisation process, e.g. from a solution of the insert material.

The lyophilisation may be effected under conventional conditions, preferably at low temperatures, e.g. ca. about -100°C to about -10°C . Conventional pressures, e.g. ca. about 0.01 mm to about 0.2 mm mercury, may be used.

Lyophilisation may produce an outer layer of very fine pores which may be spongy. This outer layer may be about 10 to 100 microns thick. If desired its formation may be avoided by effecting the lyophilisation at very low temperature. Alternatively it may be removed by rubbing.

In another aspect the nasal compositions of the invention may be in the form of a powder, e.g. based on lactose or water-absorbing, water-insoluble or water-soluble polymers.

As water-absorbing and water-soluble polymers to be used in the invention may be mentioned:-

Polyacrylates such as sodium polyacrylate, potassium polyacrylate and ammonium polyacrylate; lower alkyl ethers of cellulose such as methyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose and sodium carboxymethyl cellulose; polyvinyl pyrrolidone, amylose and preferably polyethylene-glycol e.g. of MW from 1000 to 8000, and hydroxypropyl-methyl cellulose.

As the desirable examples of water-absorbing and water-insoluble base, the following may be mentioned:-

They include, for instance, water-absorbing and water-insoluble celluloses such as microcrystalline cellulose, cellulose, α -cellulose, and cross-linked sodium carboxymethyl cellulose, water-absorbing and water - insoluble starches such as hydroxypropyl starch, carboxymethyl starch, water-absorbing and water-insoluble proteins such as gelatin, casein, ; water-absorbing and water-insoluble gums such as gum arabic, tragacanth gum and glucomannan; and cross-linked vinyl polymers such as cross-linked polyvinyl pyrrolidone, cross-linked carboxyvinyl polymer or its salt, cross-linked polyvinyl alcohol and polyhydroxyethylmethacrylate. Of these mentioned above, water-absorbing and water-insoluble celluloses and cross-linked vinyl polymers are desirable, and water-absorbing and water-insoluble celluloses are more desirable and microcrystalline cellulose is especially desirable.

The preferred polymers have characteristics as mentioned above for the nasal inserts or are conventionally employed for nasal powder administration.

Preferred hydroxypropylmethyl celluloses have a 28-30 per cent methoxyl content and a 7 -12 weight per cent hydroxypropoxyl content. A preferred example is brand Methocel E5. Viscosities are preferably from 1 to 50 cP (2% aqueous solution at 20°).

Preferably the mean polymerisation number of the preferred polymers, microcrystalline cellulose, is from about 200 to 2000, preferably 200 to 300. Preferred mean molecular weights are from about 20,000 to about 100,000 e.g. 30,000 to 50,000.

Preferably the mean particle size is from about 5 to about 80 microns, e.g. 30 to 70 microns. The preferred average particle size is 50 microns. Conveniently the untapped specific gravity is e.g. about 260 - 300 g/l. Conveniently the microcrystalline cellulose is obtained by mechanical treatment of glucose-based polysaccharides, e.g. native cellulose, optionally with acidic treatment. Their preparation is described for example in USP 2,978,446.

Preferred forms are the AVICEL brand (Registered Trade Mark of FMC Corporation). The material used was the brand Avicel PH 101 (Registered Trade Mark) available from FMC Corporation, Marcus Hook, USA. It complies with specifications given for microcrystalline cellulose in USP/National Formulary XXI.

These powders may be prepared by mixing the SMS with the particles, e.g. a polymer base in conventional manner. The particles preferably have a particle size and/or specific gravity as given above for microcrystalline cellulose.

If desired the particles may be coated. The polypeptide may be in solution, e.g. an aqueous or alcoholic solution when being mixed with the particles and the solvent evaporated, e.g. under freeze-drying or spray drying. Such drying may be effected under the conventional conditions, e.g. as described above with respect to the inserts. This gives a coating of octreotide. Alternatively the mixture may be compacted or granulated and then be pulverized and/or sieved. If desired the powder may be produced in the form of an insert e.g. as described above and then pulverized.

It is desirable in general to use a particle weight which is more than 5 times the weight of SMS, especially 10 to 100, e.g. 10 to 30, times.

Examples of loadings of SMS are 0.2, 0.4, 0.8 and 1.6 mg SMS per 20 mg powder.

Preferably the powder has a particle size of from 10 to 250 microns.

The powdery pharmaceutical composition can be directly used as a powder for a unit dosage form.

If desired the powder can be filled in capsules such as hard gelatine capsules. The contents of the capsule may be administered using e.g. an insufflator.

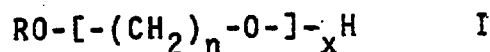
The compositions of the invention may contain other excipients. Some excipients have been described above for particular compositions, and it is to be understood that these excipients may also be present in other compositions of the invention. For example sugars, such as lactose, stabilizing agents, isotonic agents may be present in the powder form, if desired in the same preferred amounts.

If desired the compositions of the invention may also contain an absorption promoter, in particular a non-ionic promoter, suitable for application to the nasal mucosae. However, in accordance with the present invention it has surprisingly been found that, whereas where nasal administration of peptides has previously been proposed in the art, e.g. in the case of nasally administered insulin, use of a surface active agent generally improves nasal resorption or may indeed be a prerequisite for the achievement of bioavailability levels sufficient for therapeutic utility. It has in particular and most surprisingly been found that nasal SMS compositions may be prepared which contain no absorption promoter. This particular finding has the especial advantage of permitting avoidance of disadvantages otherwise encountered in the preparation of effective nasal formulations, resulting from irritant side-effects of surface active agents necessarily employed.

Where use of a nasally acceptable absorption promoter is none the less desired, e.g. substances capable of promoting absorption via the nasal mucosae may be added. Such promoters include nasally acceptable surface active agents or tensides. Such surface active agents include:-

- i. Bile acids and salts thereof, such as sodium taurocholate, sodium deoxycholate and sodium glycocholate, s-glycodeoxycholate, s-cholate, s-taurodeoxycholate.
- ii. Cationic surfactants, such as long chain amine condensates with ethylene oxide and quaternary ammonium compounds, for example cetyl trimethyl ammonium bromide and dodecyl dimethyl ammonium bromide.
- iii. Anionic surfactants such as alkylbenzenesulfonates; N-acyl-n-alkyltaurates, α -olefin sulfonates, sulfated linear primary alcohols and sulfated polyoxyethylene straight chain alcohols.
- iv. Non-ionic surfactants, such as polyoxyethylenated alkylphenols, polyoxyethylene straight chain alcohols, long chain carboxylic acid esters including glycerol esters of natural fatty acids, propylene glycol, sorbitol and polyoxyethylene sorbitol esters, e.g. Polysorbate 80^R.
- v. Amphoteric surfactants, such as imidazoline carboxylates, sulfonates etc....; and
- vi. Phospholipids, such as phosphatidyl choline etc.

Where use of a surface active agent is desired, use of nasally applicable polyoxyalkylene high alcohol ethers is preferred. Such ethers are e.g. those of formula I



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 invention are polyoxyethylene and polyoxyethylene and polyoxypropylene ethers (i.e. wherein n in the formula above is 2 or 3) in particular polyoxyethylene and polyoxypropylene lauryl, cetyl and cholesteryl ethers as well as mixtures of two or more such ethers.

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.

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.

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 Solular® (Registered Trade Mark), the companies KAO Soap, ICI and Atlas under the trade-names Emalex®, Brij® and Laureth® (Registered Trade Marks) and from the company Croda under the trade-name Cetomacrogol® (Registered Trade Mark).

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.

2.2 Solulan[®] 25 - POE, x = 25.

2.3 Solulan[®] 16 - 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:

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.

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

Preferred ethers 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.

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.

Desired viscosity for the compositions of the invention will depend on the particular form for administration, e.g. whether administration is to be by nasal drops or nasal spray.

For nasal drops an appropriate viscosity is from about 2 to 400×10^{-3} Pa.s. For nasal sprays the viscosity may preferably be less than 2×10^{-3} Pa.s.

Where a surfactant, e.g. polyoxyalkylene ether, is employed in the compositions of the invention, the amount used will vary depending on the particular surfactant chosen, the particular mode of administration (e.g. drop or spray) and the effect desired. In general however, the amount present will be of the order of from about 0.01 to 100, more preferably about 1 to 75, most preferably from about 1 to 60, mg/ml.

Compositions in accordance with the present invention may be administered in any appropriate form. The preferred forms have been described above, but it is to be understood that other formulations may be made in analogous manner or in analogy to, e.g. methods described in the literature. They may be packaged for administration in conventional manner, preferably in a nasal applicator, conveniently in such a way as to deliver a fixed dose of SMS. For administration in drop form such compositions will suitably be put up

in a container provided e.g. with a conventional dropper/closure device, e.g. comprising a pipette or the like, preferably delivering a substantially fixed volume of composition/drop. For administration as a spray, such compositions will be put up in an appropriate atomising device, e.g. in a pump-atomiser, aerosol or the like. The atomising device will be provided with appropriate means for delivery of the spray to the naris. Preferably it will be provided with means ensuring delivery of a substantially fixed volume of composition/actuation (i.e. per spray-unit). If desired the spray may be bottled under pressure in a novel aerosol device. Conveniently the device administers a metered dosage. The propellant may be a gas or a liquid, e.g. a fluorinated and/or chlorinated hydrocarbon. The spray composition may be suspended in a liquid propellant. Stabilizing and/or suspending agents may be present. If desired a powder or liquid may be filled into a soft or hard gelatine capsule. The applicator may have means to break open the capsule.

The amount of active ingredient, i.e. SMS, in the compositions of the invention may of course vary depending on a variety of factors such as the particular drug-form chosen (i.e. whether the SMS is in free, salt, solvate, or complex form) the condition to be treated, the desired frequency of administration and the effect desired. The bioavailability of the compositions of the invention may be determined in conventional manner e.g. as described in the examples hereinafter. Doses may be chosen to be equipotent to the injection route, for e.g. treatment in one of the indications mentioned above. The amount of active ingredient will generally be chosen to provide effective treatment on administration (e.g. of 1 to 5 drops, or spray-units) once or 2 to 4 x /day.

conveniently twice or more conveniently once-a-day. For this purpose the active ingredient is suitably present in a concentration such as to provide a free SMS-anniant of from about 0.1 to about 3, preferably from about 0.1 to about 1, more preferably about 0.6 to 1,mg per administration.Examples of dosages of SMS are 0.2 mg, 0.4 mg, 0.8 mg and 1.6 mg.

Individual drops or powders suitably have a volume of ca. 0.05 ml and spray units suitably ca. 0.05 to ca. 0.2 ml, e.g. ca. 0.1 ml.

Compositions thus suitably comprise from ca. 20, preferably ca. 15, more preferably ca. 10 to ca. 2.0 mg free SMS/ml, e.g. ca. 6.0 mg free SMS/ml. Where a salt, solvate or complex of SMS is employed the amount of drug substance present will be correspondingly greater. Thus where SMSac is employed, liquid compositions in accordance with the present invention may comprise e.g. ca. 7.4 mg SMSac/ml (= ca. 6.0 mg free SMS).

The following examples are illustrative of the preparation of liquid compositions in accordance with the present invention, suitable for use in a nasal spray applicator.

Further details of the characteristics of excipients may be obtained from Pharmacopeia, H.P. Fiedler, Lexikon der Hilfsstoffe, Editio Cantor, Aulendorf, 1981 and manufacturer's brochures.

EXAMPLE 1: Nasal liquid spray

Composition

	<u>INGREDIENT</u>	<u>QUANTITY/ml end composition</u>	
		A	B
1.	SMS ac	7.796 mg*	3.19 mg
	+ 5 % excess..	0.390 mg	0.16 mg
		8.186 mg	3.35 mg
2.	Glucose	50.0 mg	50.0 mg
3.	0.1N HCl.....	to pH 4.20	to pH 4.20
4.	Benzalkonium chloride	0.11 mg	0.11 mg
5.	H ₂ O (injection grade)	.. to an end volume of 1.0 ml	

* = 6.315 mg free SMS

Production

Components 1, 2 and 4 are mixed in water in conventional manner, a 5% excess of SMSac being added to allow for loss in filtration. Component 3 is then added to bring the pH to 4.2 and further water (5) added to provide the desired end-volume. The mixture is stirred for 5 mins. and filtered (0.2 micron holes) and filled with CO₂-gassing into Rexo-containers. The resultant solution is clear and colourless has an end pH of 4.2 ± 0.5 and is suitable for administration as a nasal spray from a spray dispenser device delivering ca. 0.095 ml /spray-unit (= ca. 0.6 mg/free SMS/spray unit for Example 1A and 0.25 mg/free SMS/spray unit for Example 1B).

EXAMPLE 2: Nasal liquid spray

Example 1A is repeated but with addition of 3.0 mg/ml end composition powdered SOLULAN C24 (Polyoxyethylene-(24)-cholesteryl ether) together with components 1,2 and 4 in the first production step.

BIOAVAILABILITY STUDY for EXAMPLES 1 and 2

The investigation is carried out on 12 healthy volunteers (4 females, 8 males, average age 31.5 years, average weight 68 kg, average height 183 cm) in accordance with the guidelines laid down in the Tokyo Amendment (1975) of the Declaration of Helsinki (Federal Register 40, p. 16056, April 9, 1975).

Excluded are subjects with known impairment of hepatic or renal function, heart failure or disorders of fluids and electrolytes. Further exclusion criteria are pregnancy and previous history of allergic reactions. Chronic symptoms of constipation, diarrhea or acute symptoms related to the gastrointestinal tract or acute or chronic sinusitis as well as acute infections of the respiratory tract at the time of the study are also a ground for exclusion.

An EEC (12 leads) is performed before commencing the investigation. Laboratory test (in blood: red blood cell count, hemoglobin, white blood cell count, erythrocyte sedimentation rate, platelet count, post prandial glucose; in serum: total protein and electrophoresis, sodium, potassium, creatinine, uric acid, SGOT, SGPT, γ -GT, LDH, alkaline phosphatase, cholesterol, bilirubin, α -amylase; in urine: pH, protein, glucose, sediment) are done before and at the end of the study.

Each subject receives two administrations comprising:

1. 0.6 mg free SMS administered nasally in spray form employing the composition of example 1A; and
2. 0.6 mg free SMS administered nasally in spray form employing the composition of example 2.

Administration is effected in randomized cross-over sequence. The interval between administrations is at least three days. The drug

is given in the morning after a light breakfast without caffeine-containing beverages. Each subject is instructed to administer the nasal spray with the head in the upright position into the right nostril. Before intra-nasal administration the nostrils are cleaned by blowing the nose. During and after administration of the substance the subjects refrain from taking breath for 10 seconds. At least 100 ml of water or fruit tea are drunk every hour in order to maintain a satisfactory urinary output.

Blood samples are taken immediately before SMS application, 5', 10', 15', 20', 30', 40', 50', 60', 75', 90', 2 h, 2.5 h, 3 h, 4 h, 5 h, 6 h, and 8 h after drug administration. They are drawn through a catheter introduced in the cubital vein at the beginning of the study and are put on ice in empty tubes, centrifuged about 15 - 30 minutes later at 4°C and the serum is deep-frozen at -20°C until analysed.

Urine samples are collected before drug's administration and then between 0 h - 2 h, 2 h - 4 h, 4 h - 6 h, and 6 h - 8 h. The total volume of each urine sample is measured, and about 5 ml of the urine are deep-frozen at -20°C until analysed.

Blood pressure and heart rate are monitored immediately before, 1 h, 2 h, 3 h, 4 h, 5 h, 6 h, and 8 h after drug application.

SMS 201-995 concentrations in serum and urine are analysed using radioimmunoassay technique providing a limit of detection of 0.2 ng/ml.

RESULTS

The compositions as administered are well tolerated, with side-effects (hypermotility in the abdomen/fatty stool) recorded in 4 out of 12 subjects only, and being in all cases of slight intensity only and with a maximum duration of 2 hours.

Bioavailability levels based on serum level concentration and cumulative urinary excretion indicate that therapeutic SMS serum levels are achieved employing both compositions and that treatment via nasal administration of either composition is suitable for long term clinic application.

EXAMPLE 3: Nasal SMS liquid spray

This is made up analogously to that described in Example 1 and contains:-

	mg/ml
1. SMS ac	11.55 *
+5% excess	0.55
2. Glucose	50
3. HCl 0.1N to pH	4.2
4. Benzalkonium chloride	0.11 mg
5. H ₂ O (injection grade) to an end volume of 1 ml	
* = 11 mg free SMS	

2.5 ml of the solution is filled under CO₂ gas into a 3.5 ml glass dispenser fitted with a nasal spray device. This gives 1 mg free SMS per actuation.

EXAMPLE 4: SMS nasal lyophilisate insert

A lyophilisate insert (plug) is made comprising the following:-

	mg (4A)	mg (4B)
SMSac	0.316 ¹⁾	0.315 ¹⁾
Lactose	2.0	1.0
HPMC (Pharmacoat® 606, Registered Trade Mark)	3.0	-
HPMC (Methocel E5)		1.5
PEG® (MW 4000) Registered Trade Mark)		1.5

1) Equivalent to 0.25 mg free peptide

Preparation of nasal insert from hydroxypropylmethyl
cellulose

30 g of pure water are heated to 70°C. 1.5 g of HPMC (in the case of example 4A and 0.75 g HPMC plus 0.75 g PEG 4000 in the case of example 4B) are added. The suspension is cooled to room temperature, and 1 g of lactose (200 mesh) (in the case of example 4A and 0.5 g of lactose in the case of example 4B) are added. 15 g of pure water are used to dissolve the SMS. The liquids are mixed and water added to 50 ml. The solution is filtered through 0.2 micron holes, and pipetted in 0.1 ml lots into depressions (5 mm) in an aluminium plate.

The plate is cooled to -35°C for 4 hours, then lyophilisation starts for 40 hours at -10°C and continues for 24 hours at + 15°C (in the case of example 4A and starts for 66 hours at -10°C and continues for 24 hours at + 10°C in the case of example 4B).

The resultant lyophilised blocks are, after raising the temperature in the lyophilisater to room temperature, carefully removed from the plate and inserted into a 1 ml syringe (fitted with a plunger) the needle end of which has been cut off about 3 mm from the end. Each block weighs about 5 mg.

The resultant insert is stable and easily disolvable in water. It is a uniform lyophilisate sized about 5 mm in diameter and about 6 to 7 mm in length. Under the electron microscopy it appears as a laminar ordered sheet system with long parallel pore channels of diameter about 5 to 10 microns. The edge of the lyophilisate is a layer of about 50 microns having a fine, foam-like, porous structure.

EXAMPLE 5: SMS_nasal_powder

A powder (particle size 38-68 μm (sieved)) is made up containing per 20 mg 0.3 mg SMS ac (= 0.25 mg free SMS) and 19.7 mg microcrystalline cellulose (AVICEL PH 101) (= Example 5A) or Lactose (= Example 5B). This is filled into a capsule which is nasally administered by an insufflator.

Bioavailability_Trials_in_Monkeys

Compositions were administered nasally to groups of 4 rhesus monkeys at a dose of 0.5 mg SMS. Pharmacokinetic parameters obtained:

	Cpmax	t max	AUC (0 - 6 hr)
	(ng/ml)	hr	ng ml ⁻¹ hr
Example 4A	23.60	0.25	37.25
Example 1B	2.60	0.25	13.16
Example 4B	9.54	0.25	24.80
Example 5A	55.75	0.25	77.83
Example 5B	19.96	0.25	32.14

EXAMPLE 6: Nasal lyophilisate inserts

Lyophilisate inserts A and B were made in analogous manner to Example 4 containing:-

	mg (6A)	mg (6B)
SMS ac	1.20	1.20
+ 5% excess	0.06	0.06
Lactose	1.0	2.0
HPMC (Methocel E5)	1.5	3.0
PEG 4000	1.5	-

H₂O (injection grade) up to the end volume of 1 ml.

The lyophilisates (length 5 mm, diameter 5 mm) were locally and systemically well tolerated.

EXAMPLE 7: Nasal powders

Nasal powders A and B were prepared containing:-

	mg (7A)	mg (7B)
SMS ac	1.32	1.32
+ 5% excess	0.07	0.07
Microcrystalline cellulose (Avicel PH 101 - particle size 38-68 microns)	18.61	--
HPMC (Methocel E5) particle size 38-68 microns	--	18.61
Total	20	20

These powders were prepared in a charge for about 300 unit doses by mixing the SMS and about one quarter of the polymer. The mixture is sieved. The remainder of the polymer is then added and the mass is mixed thoroughly.

If desired the SMS may be dissolved in an aqueous alcoholic solution and this is mixed with the polymer. The resultant suspension or solution is freeze-or spray-dried to give a powder.

The final powder has a particle diameter from about 20 to about 250 microns.

These powders are filled into a capsule which can be nasally administered by an insufflator. 4 actuations administer 1 mg SMS in 18 mg powder.

Local and systemic tolerability were good for the nasal powders.

BIOAVAILABILITY STUDIES for examples 6 and 7

The investigation has been carried out on 12 healthy volunteers 3 (Ex.6), or 4 (Ex.7) females, and 9 or 8 males respectively, average age 26 and 27 years, average weight 69 kg, average height 175 and 178 cm) in accordance with the guidelines laid down in the Tokyo Amendment (1975) of the Declaration of Helsinki (Federal Register 40, p. 16056, April 9, 1975).

Excluded are subjects with known impairment of hepatic or renal function, heart failure or disorders of fluids and electrolytes. Further exclusion criteria are pregnancy and previous history of allergic reactions. Chronic symptoms of constipation, diarrhea or acute symptoms related to the gastrointestinal tract or acute or chronic sinusitis as well as acute infections of the respiratory tract at the time of the study are also a ground for exclusion.

An EEC (12 leads) is performed before commencing the investigation. Laboratory test (in blood: red blood cell count, hemoglobin, white blood cell count, erythrocyte sedimentation rate, platelet count, post prandial glucose; in serum: total protein and electrophoresis, sodium, potassium, creatinine, uric acid, SGOT, SGPT, gamma-GT, LDH, alkaline phosphatase, cholesterol, bilirubin, α -amylase; in urine: pH, protein, glucose, sediment) are done before and at the end of the study.

Each subject receives two administrations comprising:

1. 1 mg free SMS administered as a nasal insert or a nasal powder employing the composition of examples 6 or 7A respectively, and
2. 1 mg free SMS administered as a nasal insert or a nasal powder employing the composition of example 6B or 7B respectively.

Administration is effected in randomized cross-over sequence. The interval between administrations is at least three days. The drug is given in the morning after a light breakfast without caffeine-containing beverages.

The nasal inserts were administered into the right nostril with an applicator. For the nasal administration of the gelatine capsules (powders) these are put into an insufflator as usually used for antiasthmatic drugs (Insuflator Intal^R nasal, Registered Trade Mark, Fisons). Four puffs are administered alternatively into the right and left nostril starting with insufflation into the right nostril. After each puff the subject inhales the administered powder. Before administration the nostrils were cleaned by one of the investigators the subject being in the sitting position.

Blood samples are taken immediately before SMS application, 5', 10', 15', 20', 30', 40', 50', 60', 75', 90', 2 h, 2.5 h, 3 h, 4 h, 5 h, 6 h, 8 h, 10 and 11 h, after drug administration. They are drawn through a catheter introduced in the cubital vein at the beginning of the study and are put on ice in empty tubes, centrifuged about 15 - 30 minutes later at 4°C and the serum is deep-frozen at -20°C until analysed.

Blood pressure and heart rate are monitored immediately before, 1 h, 2 h, 3 h, 4 h, 5 h, 6 h, and 8 h after drug application.

SMS 201-995 concentrations in serum (powders) resp. plasma (inserts) are analysed using radioimmunoassay techniques providing a limit of detection of 0.2 - 0.1 ng/ml.

Bioavailability levels based on serum and plasma level concentration and cumulative urinary excretion indicate that therapeutic SMS serum levels are achieved employing all compositions and that treatment via nasal administration of either composition is suitable for long term clinic application.

Pharmacokinetic parameters
SMS nasal (dose = 1.0 mg)
median values

Example	6A	6B	7A	7B
Tmax (min)	35.0	20.0	15.0	30.0
Cp (Tmax) (ng/ml)	1.4	2.5	26.1	3.2
AUC (0'-720')				
(ng*min/ml)	227.0	334.0	2066.0	560.0

CLAIMS

1. A nasal pharmaceutical composition comprising octreotide.
2. A composition according to claim 1 adapted to contain from 0.1 to 3 mg octreotide per dose.
3. A composition according to claim 1 adapted to contain from 0.1 to 1 mg octreotide per dose.
4. A composition according to claim 1 adapted to contain from 0.6 to 1 mg per dose.
5. A composition according to any one of claims 1 to 4 in the form of a liquid.
6. A composition according to claim 5 in the form of an aqueous solution.
7. A composition according to any one of claims 1 to 4 in the form of a nasal insert.
8. A composition according to any one of claims 1 to 4 in the form of a powder.
9. A composition according to claim 8 containing particles coated with a layer of octreotide.
10. A composition according to claim 8 or 9 wherein the powder comprises particles containing hydroxypropylmethyl cellulose.
11. A composition according to claim 8 or 9 wherein the powder comprises particles containing lactose.



12. A composition according to claim 8 or 9 wherein the powder comprises particles containing microcrystalline cellulose.
13. A composition according to any one of claims 8 to 13 comprising from 0.2 to 1.6 mg octreotide per 20 mg powder.
14. A composition according to claim 8 comprising 0.2 mg octreotide per 20 mg powder.
15. A composition according to claim 8 comprising 0.4 mg octreotide per 20 mg powder.
16. A composition according to claim 8 comprising 0.8 mg octreotide per 20 mg powder.
17. A composition according to claim 8 comprising 1.6 mg octreotide per 20 mg powder.
18. A composition according to any one of claims 8 to 17 wherein the weight ratio of octreotide to particles of powder is 1 : 10 - 100.
19. A composition according to any preceeding claim in unit dosage form.
20. A composition according to claim 19 in a capsule.
21. A composition according to any preceeding claim in a nasal applicator.
22. A composition according to claim 21 in an aerosol device.
23. A composition according to claim 22 wherein the aerosol device contains a liquid propellant.



24. A nasal octreotide composition substantially as herein-
before described with reference to any one of the examples.

25. Use of octreotide in the manufacture of a nasal pharma-
ceutical composition as claimed in any one of claims 1 to 24.

