100-6939/II

PHARMACEUTICAL COMPOSITIONS CONTAINING ANTI-SEROTONIN INDOLYL DERIVATIVES

This invention relates to new uses and modes of administration of $5HT_3$ antagonists, and in particular indol-3-yl-carboxylic acid endo-8-methyl-8-aza-bicyclo [3,2,1]oct-3-yl ester, (hereinafter the compound of the invention also known as ICS 205-930).

The compound may be used in any pharmaceutically acceptable form, including the free base and in acid addition and quaternary ammonium salt forms.

The compounds of the invention is known for example from Belgian patent 897,117. The compound is described therein as being a $5HT_3$ receptor antagonist or serotonin M receptor antagonist (serotonin M receptors have been reclassified as $5HT_3$ receptors).

The compound is indicated for use as an anti-migraine agent, anti-arrhythmic, and for treatment of serotonin-induced gastro-intestinal disorders including emesis, e.g. induced by anti-cancer agents.

We have now discovered that the compound has interesting new uses as described and claimed below and in copending application No. 8717768 (GB 2,193,633). These uses for other 5-HT_3 antagonists are claimed in our copending application 9008069 (GB 2231265).

The antagonistic action against 5-HT_3 receptors of the preferred compound ICS 205-930 (indol-3-yl carboxylic acid endo-8-methyl-8-

aza-bicyclo[3,2,1]oct-3-yl ester) on the rabbit vagus, rabbit heart and guinea pig ileum has been described (P.Donatsch et al., Br.J. Pharmacol. 1984, 81, 348), and also its topical application to humans as the first 5-HT_3 antagonist.

In the Belgian Patent No. 897,117 it was also stated that the compounds disclosed therein are indicated as anti-psychotics.

In a first aspect the invention provides:

a) Use of indol-3-yl-carboxylic acid endo-8-methyl-8-aza-bicyclo [3,2,1]oct-3-yl ester, in free base form, or in pharmaceutically acceptable acid addition salt form, or in pharmaceutically acceptable quaternary ammonium salt form, in the manufacture of a medicament suitable for the treatment of rhinitis or serotonin-induced nasal disorders or for co-administration in therapy with another active agent to increase the bioavailability thereof, or for nasal administration in therapy, or

b) Indol-3-yl-carboxylic acid endo-8-methyl-8-aza-bicyclo [3,2,1]oct-3-yl ester in free base form, or in pharmaceutically acceptable acid addition salt form, or in pharmaceutically acceptable quaternary ammonium salt form, for use as a combined preparation for simultaneous, separate or sequential use for co-administration in therapy with another active agent to increase the bioavailability thereof, or for nasal administration in therapy.

c) Use of indol-3-yl-carboxylic acid endo-8-methyl-8-aza-bicyclo [3,2,1]oct-3-yl ester in free base form, or in pharmaceutically acceptable acid addition salt form, or in pharmaceutically acceptable quaternary ammonium salt form, in the manufacture of a medicament for the treatment of lung embolism.

d) A composition containing indol-3-yl-carboxylic acid endo-8-methyl-8-aza-bicyclo [3,2,1]oct-3-yl ester in free base

form, or in pharmaceutically acceptable acid addition salt form, or in pharmaceutically acceptable quaternary ammonium salt form, with another active agent.

We have found that the compound of the invention may be administered nasally and has an especially interesting resorption profile.

Furthermore, the compound of the invention increases the nasal resorption or bioavailability of other active agents such as peptides particularly when administered by the nasal route.

The compound of the invention moreover is useful in the treatment of rhinitis and serotonin-induced nasal disorders as indicated by an inihibition of nasal secretions on administration of the compound of the invention.

The testing may be effected as follows:-

The biovavailability and pharamcokinetic profile of the compound of the invention may be determined in conventional manner, e.g. in mammals including rhesus monkeys and humans. The concentration of the compound of the invention in the blood plasma after administration of from about 0.01 to about 10 mg/kg to each nostril, e.g. 7.5 mg locally to the nasal mucous membrane, e.g. as a spray, may be determined in conventional manner by e.g. radioimmunoassay or HPLC methods. The compound of the invention is rapidly absorbed, e.g. over about 10 minutes.

Even after ca. 5 to 10 minutes following nasal administration, 200 ng of the compound indole-3-yl-carboxylic acid endo-8-methyl-8-aza-bicyclo [3,2,1]oct-3-yl ester may be detected in 1 ml of plasma. Upon oral administration, this concentration of active ingredient in the plasma is reached only after ca. 30 to 40 minutes. The general bioavailability of the compound of the invention over a period of 6

hours is the same for nasal administration as for oral administration.

Nasal secretions are also inhibited. Additionally, the compound of the invention when administered, e.g. at a dose of from 0.01 to 10 mg/kg with a therapeutically effective dosage of another compound, e.g. a peptide, such as salmon calcitonin increases the absorption thereof.

For example, in the case of the compound of the invention (15 mg) and salmon calcitonin (100 IU) half of which is applied to each nostril, the bioavailability of salmon calcitonin (AUC up to 2 hours) is increased from 0.08 IU/ml/hr plasma to 1.632 mIU/ml/hr/plasma in the rhesus monkey.

For the rhinitis and nasal serotonin-induced disorder indications, the appropriate dosage will, of course, vary depending upon, for example, the host, the mode of administration and the nature and severity of the condition being treated. However, in general, satisfactory results are indicated to be obtained at daily dosages from about 0.01 mg/kg to about 10 mg/kg animal body weight. In humans, an indicated daily dosage for oral administration is in the range from about 5 mg to about 300 mg of the compound conveniently administered, for example, in divided doses up to four times a day, e.g. in the range of about 40 mg p.o.

When the compound of the invention is co-administered with another active agent, the appropriate dosage will, of course, vary depending upon, for example, the other active agent employed, the host, the mode of administration and the nature and severity of the condition being treated. However, in general, satisfactory results are indicated to be obtained at daily dosages from about one half to one tenth the usual dose of the other active agent. The compound of the invention is indicated to be administered at about one half to one tenth the usual dose.

The compound of the invention may be administered for the rhinitis and nasal serotonin-induced disorders and for co-administration with

another active agent, e.g. a peptide, by any conventional route, in particular enterally, preferably orally, e.g. in the form of tablets or capsules, or parenterally e.g. in the form of injectable solutions or suspensions. The local application by the nasal route is preferred.

For the nasal administration route, the appropriate dosage will, of course, vary depending upon, for example, the nature and severity of the condition being treated. However, in general, satisfactory results in animals are indicated to be obtained at daily dosages from about 0.001 mg/kg to about 10 mg/kg animal body weight. In humans, an indicated dosage per actuation is in the range from about 0.01 mg to about 1 mg of the compound of the invention conveniently administered, for example, in doses up to four times a day.

Thus for gastrointestinal disorders or for migraine prophylaxis the compound according to the invention is indicated to be administered to the body nasally in a dosage of 0.13 to 0.4 mg/kg body weight, i.e. ca. 10 to 30 mg or 1 to 3 pumps of the nasal spray per patient, and in order to control arrhythmia, it should be given in a dosage which is ca. 10 times higher, i.e. from 1.3 to 4 mg per kg body weight or 100 to 300 mg, or resp. 10 to 30 pumps of the nasal spray per patient.

The compound indicated to be administered at daily dosages of about 0.1 mg nasally to humans.

The compound of the invention may be administered nasally in any pharmacologically active form, e.g. in free base form, in acid addition salt form or in quaternary ammonium salt form.

The nasal mode of administration creates a simple method of administration which rapidly gives results and can be easily carried out by the patient himself, e.g. by administering a liquid form for nasal administration, for example, a nasal spray or drop solution using a nasal applicator, or by inserting a gelatinous sponge or lyophilisate soaked in the active substance, or by blowing the galenic form in powder form into the nostrils.

The compound of the invention may be present in the liquid form for nasal administration in a proportion of 1 to 30%, preferably 5 to 20%, especially 10 to 15% (weight/volume).
The present invention accordingly provides also to a liquid form for nasal administration, containing

1) the compound of the invention
2) a preservative, especially benzalkonium chloride, and
3) a liquid diluent or a carrier, suitable for application to the nasal mucous membrane.

The proportion of benzalkonium chloride in the compositions according to the invention is preferably, ca. 0.002 to ca. 0.02, especially ca. 0.01% (weight/volume) of the total composition.

In accordance with the invention, the above-mentioned forms of administration may be administered to the nasal mucous membrane, e.g. as drops or as a spray. As described hereinafter, however, they are preferably administered as a spray, i.e. as finely dispersed droplets. One further possible way of bringing the above-mentioned liquid form for nasal administration into contact with the nasal mucous membrane is to soak a gelatinous sponge (SPONGOSTAN - SPONGOSTAN as used herein is a Registered Trade Mark) or lyophilisate with the substance and then to insert the sponge into the nostrile.

The liquid diluent or carrier employed is conveniently water (pharmaceutical grade). An aqueous salt solution is preferred in particular. The liquid forms for nasal administration according to the invention are formulated such that they allow administration to be effected nasally. With this in mind, they can e.g. also contain minimal amounts of further desired components or excipients, e.g. additional preservatives, or e.g. ciliary stimulants such as caffeine.

The liquid forms for nasal administration according to the invention preferably have a pH value of 5.5 to 6.

The liquid forms for nasal administration should also have an appropriate isotonicity and viscosity. They preferably have an osmotic pressure of ca. 260 to ca. 380 mOsm/litre. The desired viscosity of the compositions according to the invention depends on the relevant form of administration, e.g. whether nasal drops or a nasal spray are administered. For nasal drops, a viscosity of ca. 2 to ca. 40 x 10^{-3} Pa.S is suitable.

If desired, the liquid forms for nasal administration may also contain further components, especially conventional pharmaceutically available surface-active agents. In this connection and as a further aspect of the present invention, it was found that the use of surface-active compounds in the nasal administration of the compounds of the invention increases their resorption through the nasal mucous membrane and improves the initial bio-availability. In this case, preference is given to non-ionic surface-active agents, for example polyoxyalkylene ethers of higher alcohols, e.g. of the general formula,

$$RO[-(-CH_2)_n-O-]_xH$$

wherein RO signifies the radical of a higher alcohol, especially a higher alkanol such as lauryl or cetyl alcohol, or of an alkylephenol, or a sterol, especially lanosterol, dihydrocholesterol or cholesterol, as well as mixtures of two or several such ethers. Preferred polyoxyalkylene ethers which can be used for the present invention are polyoxyethylene- and polyoxypropylene-ethers (i.e. wherein n in the above-mentioned formula is 2 or 3), espcially lauryl-, cetyl- and cholesterylpolyoxyethylene and -polyoxypropylene-ethers, as well as mixtures of two or several such ethers.

Especially suitable polyethers for use according to the invention are those in which the average value of the recurring units in the polyoxyalkylene component (x in the above formula) lies between 4 and

75, especially between 8 and 30 and particularly between 16 and 26. The polyethers may be obtainend in accordance with known methods. A large choice of such products is available commercially and is sold e.g. by Amerchol under the trade name Solulan, by KAO Soap, ICI and Atlas under the trade names Emalex, Brij and Laureth and by Croda under the trade name Cetomacrogol. [SOLULAN, EMALEX and LAURETH as used herein are Registered Trade Marks].

Examples of polyoxyalkylene ethers which are suitable for use according to the invention, e.g. (POE = polyoxyethylene ethers: POP = polyoxypropylene ether; x = average value of the recurring units in the POE/POP components) are listed in the following:-

1. Cholesterylethers:
1.1 Solulan C-24 - POE, x = 24

2. Ethers of lanolin alcohols:
2.1 Solulan 16 - POE, x = 16
2.2 Solulan 26 - 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 - partly acetylated
2.6 Solulan 97 - POE, x = 9 - wholly acetylated

3. Laurylethers:
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. Cetylethers:
4.1 Cetomacrogol - POE, x = 20 to 24

Lanolin alcohols are also known as wool fat alcohols and are a mixture

of cholesterol, dihydrocholesterol and lanosterol.

Preferred polyethers for use according to the invention are cholesteryl polyoxyethlyene ethers, e.g. polyethers of the above formula, wherein n = 2 and Ro is a cholesteryl radical, in particular polyethers wherein the number of recurring units in the polyoxyethylen component is 16 to 26, especially about 24.

These polyethers are preferably free from impurities, and especially from other polyoxyalkylene ethers. They preferably contain at least 75%, most particularly at least 85% and especially at least 90% (weight) of the pure cholesteryl polyoxyethylene ether.

If a surface-active agent, e.g. a polyoxyalkylene ether, is used, the amount present in the compositions according to the invention will depend on the surface-active agent used in particular, the form of administration (e.g. drops or spray) and the desired effect.

In general, the amount of surface-active employed is between ca. 2.0 and ca. 200 (preferably up to ca. 100, especially up to ca. 20), especially between ca. 5 and ca. 30 (preferably up to ca. 15) and in particular ca. 10 mg/ml.

For nasal administration, the liquid forms for nasal administration are preferably placed in an applicator, which is equipped with a device that enables the composition to be applied to the nasal mucous membrane, e.g. a nasal spray applicator.

Such applicators are known per se and include those which are suitable for the administration of liquid preparations as drops or as a spray to the nasal mucous membrane. Since the dosing of the compounds of the invention should be as exact as possible, the use of spray applicators in which an exact control over the quantity administered is possible is generally preferred.

Suitable appliances for administration are e.g. atomizers such as pump

dispensers or aerosol cans. In the latter case, the applicator contains a composition according to the invention as well as a propellant which is suitable for use in a nasal spray applicator. The atomizer applicance is provided with an appropriate spray device which enables the composition to be applied to the nasal mucous membrane. Such devices are known in general.

The container, e.g. a nasal spray applicator, may contain a quantity of the composition which is sufficient for a single nasal dose or for administration several doses, e.g. over a period of several days or weeks. The amounts of the individual doses will preferably correspond to the above-mentioned doses.

Applicators as defined above are preferably spray applicators for nasal usage. They preferably enable the composition contained therein to be administered in single doses of ca. 0.05 to ca. 0.15 ml, e.g. ca. 0.1 ml.

Suitable compositions, as well as the individual components 1,2 and 3 for use in an applicator, are those which have been previously described. The dosages which are suitable for use similarly correspond to the dosages given previously.

Furthermore, the invention relates to a process for the production of a liquid form for nasal administration, containing

1) the compound according to the invention
2) a preservative, especially benzalkonium chloride, and
3) a liquid diluent or a carrier, which is are suitable for administering to the nasal mucous membrane, as well as optionally a surface-active agent which is suitable for administering to the nasal mucous membrane, characterised in that the components are intimately mixed together, and if desired, the composition obtained is placed in an applicator which is provided with a spray device which enables the composition thus obtained to be administered to the nasal mucous membrane.

Furthermore, a sponge (SPONGOSTAN) may be soaked with the composition obtained and the soaked sponge can be inserted into the nostrils.

The stability of the composition according to the invention can be determined in the usual way.

The compositions according to the invention containing benzalkonium chloride are stable towards contamination by germs, e.g. as in standard tests such as those described by S.Urban et al., in Zbl. Bakt.Hyg. I.Abt. Orig. B 1972, 478-484 (1981) and S.Urban, Acta Pharma. Technol. 22, 247-253 (1976).

For example, the cell count of the standard bacteria, namely E.coli ATCC 7839, Pseud. aeruginosa ATC 9027, Staph.aureus ATCC 6538, Strept. pyogenes ATCC 8668 and standard fungi Cand.albicans ATCC 10231, Sacch.cerevisae ATCC 9763, Aspergillus niger ATCC 16404 and Pen.steckil ATCC 10499, is reduced to 0.1% or less within 24 hours after injecting them with the composition, as can be shown in standard tests.

In a stability test, the nasal spray composition of the following example 1 was kept for 3 months at 30°C 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. cerevisysae ATCC 9763, Aspergillus niger ATCC 16404 and Pen.stechii ATCC 19499 were added until a cell count of ca. 2×10^5 organisms was reached in the injected liquid. Within 2 hours, the germ count had reduced to less than 0.1%. Within 4 weeks, the germs could no longer be detected.

Equally favourable results are obtained if the compounds of the invention are administered in a galenic form, which is in the form of a powder and is introduced by blowing into the nostrils.

The compound of the invention antagonises the pulmonary depressor

reflex in animals.

The action of the compound may be observed in spontaneously breathing rabbits which are anaesthetized by a continuous infusion of sodium pentobarbital. Both vagi are intact and the systemic, arterial blood pressure, heart beat, breathing rate and platelet count are normal.

Pulmonary embolism is produced by injecting 1 mg Sephadex G-^{25} beads suspended in 0.2 ml dextran (6%) in 1 minute intervals in 6 animals into the right atrium.

Pretreatment with the compound of the invention i.v. at a dose of from 0.1 to 1 mg/kg produces a reduction in mortality and an improvement in the cardiovascular and breathing reflex parameters resulting during the developing lung embolism.

For this indication, the appropriate dosage will, of course, vary depending upon, for example, the host, the mode of administration and the nature and severity of the condition being treated. However, in general, satisfactory results in animals are indicated to be obtained at daily dosages from about 0.1 mg/kg to about 5 mg/kg animal body weight. In larger mammals, for example humans, an indicated daily dosage is in the range from about 5 mg to about 50 mg of a compound of the invention conveniently administered, for example, in divided doses up to four times a day, preferably parenterally.

The compound is preferably administered in the form of a pharmaceutical composition e.g. as described above.

The compound of the invention may be administered for the lung embolism, by any conventional route, in particular enterally (if appropriate), preferably orally, e.g. in the form of tablets or capsules, or parenterally (if appropriate), e.g. in the form of injectable solutions or suspensions, or by the nasal route.

The compound of the invention also inhibits cancer therapy induced

emesis in animals as indicated by standard tests, e.g. an inhibition of cis-platinin (10 mg/kg i.v.) induced emesis in ferrets at a dose of from about 0.005 to about 0.5 mg/kg i.v.

The compound of the invention furthermore is useful in the treatment of other $5HT_3$-induced gastro-intestinal disorders, e.g. as indicated in activity in tests indicating in EP 189,002 at the same order of activity.

The compound is useful in the treatment of disorders resulting from increased peristaltic movements in the intestines and intestinal disorders arising or from activation of 5-HT_3 receptors, including diarrhea, e.g. sercretory diarrhea, bacterial induced diarrhea, choleic diarrhea, traveller's diarrhea and psychogenic diarrhea, Crohn's disease, spastic colon and irritabel bowel syndrome. The compounds are also indicated to be useful in the treatment of disorders due to hypersecretion in the intestines, e.g. as a result of inflammation such as arising out of gastritis, peptic ulcer, biliary dyskinesia, appendicitis, ulcerative colitis and due to carcinoid syndrome leading to increased 5-HT secretion.

Furthermore, the compound is useful in the treatment of disorders arising from decreased peristaltic movements in the stomach and/or stomach disorders arising from activation of 5-HT_3 receptors, including those arising from decreased gastric emptying, including treatment oesophageal motility disturbances, achalasia, hiatus hernia, cardiac insufficiency, gastro-oesophageal and gastro-duodenal reflux, stomach hypotonia and pylorus hyperplasia.

The compound is moreover useful in treatment of schizophrenia and mania and anxiety.

For all these indications, the compound may be administered in the same manner as for the rhinitis indications and in the same manner as described in European Patent Publication No. 189,002.

Toxicity and Tolerability:

Toxicity and Tolerability studies may be effected in conventional manner with the compound of the invention to determine the upper dosage.

Toxicity studies may be effected for example in the rat and the dog over for example 26 weeks.

For the compound of the invention over 26 weeks the no toxic effect level in the dog was 5-20 mg/kg/daily p.o. For the rat it was 16 to 45 mg/kg per day p.o.. In healthy human volunteers single doses up to 150 mg were well tolerated without relevant side effects.

The following examples illustrate the invention.

EXAMPLE 1: Tablets for oral administration

Tablets concerning the consituents as specified below were produced in conventional manner and are used in the indications specified above.

Compound of the invention in form of hydrochloride (corresponding to 15 mg free base)	16.9 mg
Hydroxy-propyl-cellulose	1.2 mg
Corn Starch	12.0 mg
Lactose	92.8 mg
Silica	0.6 mg
Magnesium stearate	1.5 mg
Tablet weight	125.0 mg

EXAMPLE 2: Injection solution for i.v. administration

A composition for injection is made up in conventional manner and is used at a dose of 10 mg a day.

	A	B	C
Compound of the invention in form of hydrochloride	1.13[1]	2.256[2]	11.282[3]
Acetic acid (99 to 100%)*	1.2	0.6	0.6
Sodium acetate 3. H_2O*	1.8	3.18	3.18
Sodium chloride	8	7.5	6.5
Water for injection to	1.0 ml		

[1] = 1 mg free base
[2] = 2 mg free base
[3] = 10 mg free base

pH value 4.3; *Buffer used 1/30 molar

EXAMPLE 3: Capsules for oral administration

5 mg and 15 mg capsules (A and B respectively) containing the constitutents as specified below were produced in conventional manner and are used in the indication specified above 2 - 4 times a day in the case of A and once a day in the case of B.

	A mg	B mg
Compound of the invention in form of hydrochloride	5.641	16.92
Lactose 200 mesh	84.929	79.29
Lactose 100 mesh	84.43	79.29
Corn starch	120.00	120.00
Silica	1.5	1.5
Magnesium stearate	3.0	3.0
	300 mg	300 mg

Capsules containing other weights can be formulated in conventional manner.

EXAMPLE 4: Nasal liquid Compositions

Components	Quantity of components
Indol-3-yl carboxylic acid-endo-8-methyl-8-aza-bicyclo[3,2,1]oct-3-yl ester. HCl	100 mg
benzalkonium chloride	0.1 mg
NaCl (0.9% aqueous solution)	0.6 ml
distilled water	0.4 ml

The solution obtained is filtered (e.g. through a 0.2 um filter) and filled into a nasal canister, or a gelatinous form (SPONGOSTAN) is soaked with the solution. It is administered e.g. for the treatment of

rhinitis, lung embolism or to improve the absorption of other active agents.

CLAIMS

1. Use of indol-3-yl-carboxylic acid endo-8-methyl-8-aza-bicyclo [3,2,1]oct-3-yl ester in free base form, or in pharmaceutically acceptable acid addition salt form, or in pharmaceutically acceptable quaternary ammonium salt form, in the manufacture of a medicament suitable for the treatment of rhinitis or serotonin-induced nasal disorders or for co-administration in therapy with another active agent to increase the bioavailability thereof, or for nasal administration in therapy.

2. Indol-3-yl-carboxylic acid endo-8-methyl-8-aza-bicyclo [3,2,1]oct-3-yl ester in free base form, or in pharmaceutically acceptable acid addition salt form, or in pharmaceutically acceptable quaternary ammonium salt form, for use as a combined preparation for simultaneous, separate or sequential use for co-administration in therapy with another active agent to increase the bioavailability thereof, or for nasal administration in therapy.

3. Use according to claim 1 in the manufacture of a medicament suitable for serotonin-induced nasal disorders in therapy.

4. Use according to claim 1 in the manufacture of a medicament suitable for the treatment of rhinitis.

5. Use according to claim 1 in the manufacture of a medicament suitable for co-administration in therapy with another active agent to increase bioavailability thereof.

6. Use according to claim 1 in the manufacture of a medicament suitable for nasal administration in therapy.

7. Use according to claim 2 for nasal administration in therapy.

8. Use according to claim 1 in the manufacture of a medicament suitable for nasal co-administration with another active agent.

9. A nasal composition containing indole-3-yl-carboxylic acid endo-8-methyl-8-aza-bicyclo [3,2,1]oct-3-yl ester in free base form, or in pharmaceutically acceptable acid addition salt form, or in pharmaceutically acceptable quaternary ammonium salt form.

10. A nasal composition according to claim 9 containing another active agent.

11. Use of indol-3-yl-carboxylic acid endo-8-methyl-8-aza-bicyclo [3,2,1]oct-3-yl ester in free base form, or in pharmaceutically acceptable acid addition salt form, or in pharmaceutically acceptable quaternary ammonium salt form, in the manufacture of a medicament suitable for the treatment of lung embolism.

12. A nasal applicator containing a nasal composition according to claim 9 or 10.

13. A composition containing indol-3-yl-carboxylic acid endo-8-methyl-8-aza-bicyclo [3,2,1]oct-3-yl ester in free base form, or in pharmaceutically acceptable acid addition salt form, or in pharmaceutically acceptable quaternary ammonium salt form, with another active agent.

14. A composition of claim 13 wherein the other active agent is a peptide.

15. A liquid nasal composition containing indol-3-yl-carboxylic acid endo-8-methyl-8-aza-bicyclo [3,2,1]oct-3-yl ester in free base form, or in pharmaceutically acceptable acid addition salt form, or in pharmaceutically acceptable quaternary ammonium salt form, a preservative and a liquid diluent or carrier.