PATENT SPECIFICATION (11) 1230472

1230472

NO DRAWINGS

(21) Application No. 31283/68 (22) Filed 1 July 1968

(31) Convention Application No. 9774 (32) Filed 10 July 1967 in

(33) Switzerland (CH)

(45) Complete Specification published 5 May 1971

(51) International Classification A 61 k 25/00

(52) Index at acceptance

A5B 26Y 310 31Y 343 34Y 38Y 393

(54) PHARMACEUTICAL PREPARATIONS HAVING AN ADRENOCORTICOTROPIC ACTIVITY

(71) We, CIBA-GEIGY AG (formerly known as CIBA Limited), a body corporate organised according to the laws of Switzerland, of Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention provides pharmaceutical preparations having an adrenocorticotropic activity which are suitable for resorption through the mucous membranes of the mouth or nose.

It has been found that adrenocorticotropically active peptides, for example the natural corticotropins and synthetic ACTH-active peptides, on administration through the mucous membranes of the mouth or nose, develop a good activity when used in the form of non-aqueous, especially oily, suspensions or solutions.

Therefore, the preparations of the invention suitable for buccal or nasal administration are characterised in that they contain the ACTH-active peptides in the form of non-aqueous, especially oily, suspensions or solutions.

Suitable non-aqueous suspending agents or solvents are those which are physiologically acceptable and tolerated by the buccal and nasal mucous membranes, more specifically monoesters of lower alkanols having 2 to 3 carbon atoms or sorbitan - polyoxyethylene - glycol with fatty acids having 8 to 22 carbon atoms, diesters of polyoxyethyleneglycol with fatty acids having 8 to 22 carbon atoms, triesters of glycerol with fatty acids having 8 to 12 carbon atoms and mixtures of any two or more of such compounds, for example ethyloleate, isopropylmyristate, isopropyl - palmitate or the triglicyeride mixtures of fatty acids with 8 to 12 or 8 to 10 carbon atoms marketed under the trade names "Miglyol 812" and "Labrafac WL 1349", and also mixtures of fatty acid esters of glycerol and of polyhydroxyethylene, for example "Labrafac WL 1219" or "Lagrafil M 2735" (the latter is an oleic acid ester); or sorbitan fatty acid esters for example "Arlacel" or "Tween" (polyhydroxyethylene - sorbitan - monooleate) if desired with addition of emulsifiers. ("Arlacel" and "Tween" are Trade Marks).

As ACTH-active peptides there may be mentioned the natural adrenocorticotropic hormones, for example β - corticotropin, and ACTH-active synthetic peptides having a shorter aminoacid chain which may be varied insofar as individual aminoacids are concerned, and also derivatives, salts and complexes of these peptides.

Synthetic ACTH-active peptides are, for example those which contain at least 16, preferably 18 to 28, aminoacids calculated from the amino-terminal end of β - corticotropin and may have some aminoacids in a different sequence. Thus, one or more of the amino acids 1 to 5, 17, 18 and 25 especially may be replaced by aminoacids other than those corresponding to the natural sequence, for example replacement of the serine residues serine^{1} and/or serine^{3} by glycine or alanine; tyrosine^{2} by phenylalanine; methionine^{4} by norvaline, leucine, norleucine or γ - amino - butyric acid; glutamic acid^{5} by glutamine; arginine^{17,18} by ornithine ^{17,18} or lysine^{17,18}; the aminoacid^{25} by valine. Serine^{1} may also be replaced by proline, threonine or other aminoacids, or it may be absent, or further aminoacid residues may precede it.

The preparations of the invention preferably contain ACTH-active peptides, the first aminoacid of which has the D-configuration, that is to say, for example, D-alanine, D-proline,, D-theonine or primarily D-serine.

ACTH-active peptides suitable for the preparations are, for example D - Ser^{1} - cortico - tropin - Arg^{18} - amide, D - Ser^{1} - Orn^{17,18} - β^{1-18} - corticotropin - Orn^{18} - amide, D - Ser^{1} - Gly^{3} - Lys^{17,18} - β^{1-18} - corticotropin - Lys^{18} - amide, D - Ser^{1} - Nle^{4} - Lys^{17,18} - β^{1-18} - corticotropin - Lys^{18} - amide, D -

Ser[1] - Lys[17,18] - β^{1-18} - corticotropin, β^{1-19} - corticotropin, D - Ser[1] - β^{1-19} - corticotropin, β^{1-19} - corticotropin - Pro[19] - amide, Glu$(NH_2)^5$ - β^{1-19} - corticotropin, D - Ser[1] - Lys[17,18] - Val[19] - β^{1-19} - corticotropin - Val[19] - amide, D - Ser[1] - Nle[4] - Lys[17,18] - Val[19] - β^{1-19} -corticotropin - Val[19] - amide, β^{1-20} - corticotropin - Val[20] - amide, D - Ser[1] - β^{1-20} - corticotropin - Val[20] - amide, D - Ser[1] - Lys[17,18] - β^{1-20} - corticotropin - Val[20] - amide, α - amino - butyryl[4] - Glu$(NH_2)^5$ - β^{1-20} - corticotropin - Val[20] - amide,, D - Ser[1] - Lys[17,18] - β^{1-19} - corticotropin - Pro[19] - amide, α - aminobutyryl[4] - β^{1-20} - corticotropin - Val[20] - amide, β^{1-21} - corticotropin, D - Ser[1] - Lys[17,18] - β^{1-21} - corticotropin - Lys[21] - amide, D - Ser[1] - Lys[17,18] - β^{1-22} - corticotropin - Val[22] - amide, β^{1-23} - corticotropin, β^{1-23} - corticotropin - Tyr[23] - amide, D - Ser[1] - β^{1-23} - corticotropin - Tyr[23] - amide, D - Ser[1] - Ala[3] - β^{1-23} - corticotropin - Tyr[23] - amide, Gly[1] - β^{1-23} - corticotropin - Tyr[23] amide, D - Ser[1] - Lys[17,18] - β^{1-23} - corticotropin - Tyr[23] - amide, β^{1-24} - corticotropin - Glu$(NH_2)^5$ - β^{1-24} - corticotropin, D - Ser[1] - Orn[17,18] - β^{1-24} - corticotropin, Gly[1,3] - β^{1-24} - corticotropin, Orn[17,18] - β^{1-24} - corticotropin, Lys[17,18] - β^{1-24} - corticotropin, D - Ser[1] - Nle[4] - β^{1-24} corticotropin, D - Ser[1] - β^{1-24} - corticotropin, D - Ala[1] - β^{1-24} - corticotropin, D - Ser[1] - Gly[3] - Lys[17,18] - β^{1-24} - corticotropin, D - Ser[1] - Nle[4] - Lys[17,18] - β^{1-24} - corticotropin - Pro[24] - amide, D - Ser[1] — Orn[17,18] - β^{1-24} - corticotropin - Pro[24] - amide, D - Ser[1] - Nle[4] - Orn[17,18] - β^{1-24} - corticotropin - Pro[24]- amide, D - Ser[1] - Gly[3] - Lys[17,18] - β^{1-24} - corticotropin - Pro[24] - amide, D - Ser[1] - Lys[17,18] - β^{1-24} - corticotropin, D - Ser[1] - Lys[17,18] - β^{1-24} - corticotropin - Pro[24] - amide, D - Ser[1] - Nle[4] - Val[25] - β^{1-25} - corticotropin - Val[25] - amide, D - Ser[1] - Nle[4] - D - Val[25] - β^{1-25} - corticotropin - D - Val[25] - amide, D - Ser[1] - Nva[4] - Lys[17,18] - Val[25] - β^{1-25} - corticotropin - Val[25] - amide, D - Ser[1] - Nle[4] - Lys[17,18] - Val[25] - β^{1-25} - corticotropin - Val[25] - amide, Nle[4] - Val[25] - β^{1-25} - corticotropin - Val[25] - amide, Nva[4] - Val[25] - β^{1-25} - corticotropin - Val[25] - amide, Nle[4] - Lys[17,18] - Val[25] - β^{1-25} - corticotropin - Val[25] - amide, β^{1-26} - corticotropin, β^{1-28} - corticotropin, β^{1-30} - corticotropin, β^{1-31} - corticotropin, β^{1-39} - corticotropin, D - Ser[1] - β^{1-39} - corticotropin, Gly[1] - β^{1-39} - corticotropin, and especially D - Ser[1] - Lys[17,18] - β^{1-18} - corticotropin - Lys[18] - amide.

The derivatives are preferably amides, especially C-terminal amides whose amide group is unsubstituted.

Particularly suitable salts of the adreno - corticotropically active peptides are the acid addition salts of physiologically tolerable acids, for example hydrochloric, acetic, sulphuric, or methanesulphonic acid, and fatty acids having a long carbon chain, for example, capric, myristic, palmitic, stearic or oleic acid.

Suitable complexes are those with inorganic or organic substances which are capable of prolonging the activity of the peptides, for example complexes with sparingly soluble zinc compounds, for example zinc hydroxide and/or zinc phosphate, with alkali metal polyphosphates, with oxypolygelatin, with polyphenols or polyalcohols, preferably polyphloretine phosphate and phytic acid, and also with polymers of aminoacids, for example prot - amine and polyglutamic acid.

The peptides, their derivatives, salts or complexes can be administered in the form of suspensions or solutions. They are advantageously used in the form of sprays or aerosols, preferably with a propellant gas. Suitable propellant gases are preferably pharmaceutically useful halogenated hydrocarbons for example the products known by the name "Freon" (Trade Mark), for example "Freon 11" (trichlorofluoromethane), "Freon 12" (dichlorodifluoromethane) or "Freon 114" (dichlorotetrafluoroethane) or mixtures thereof.

The pharmaceutical preparations may further contain assistants, for example, preserving, stabilizing, wetting or emulsifying agents.

The following Examples illustrate the invention:

Example 1

0.25 Gram of finely ground β^{1-24} corticotropin (grain size below 5.0μ) is suspended in a mixture of 3.5 ml of "Miglyol 812" and 0.08 g. of benzyl alcohol. This suspension is charged into a container with dosing valve. 0.5 ml of "Freon 12" are then pressed through the valve into the container. The "Freon" is dissolved in the Miglyol+benzyl alcohol mixture by agitation. This spray-container contains about 100 doses.

Example 2

30 mg of finely ground D - Ser[1] - Lys[17,18] - β^{1-18} - corticotropin - Lys[18] - amide (cf. Indian Patent Application No. 102,799/65) are suspended in a mixture of 75 mg of benzyl alcohol and 1.395 g. of "Miglyol" 812. A 10 ml aluminium monoblock container is filled with the suspension and is then closed with a dosing valve. After that, 6.0 g. of Freon 12/114 (40:60) are pressed in under nitrogen. The aluminium container with a content of 7.5 g contains 100 doses of 0.3 mg of peptide-amide. The valve is so adjusted that if it is pressed once, a single dose is released.

Other nasal sprays are prepared in the same manner. Instead of "Miglyol", they contain the same quantity of isopropylmyristate or isopropylpalmitate or "Labrafac WL 1219" (a mixture of glycerol- and polyoxyethylene glycol esters of fatty acids with 8 or 10 carbon atoms).

EXAMPLE 3

In a manner similar to that described in Example 2, a spray container for 100 doses is prepared. At contains:

D-Ser^1-Lys^{17,18}-β^{1-18}-corticotropin-Lys^{18}-amide	100 mg
benzyl alcohol	75 mg
Miglyol or an ester mentioned in Example 2	1325 mg
Freon 12/114 (40:60)	6000 mg

EXAMPLE 4

In a manner similar to that described in Example 2, a nasal spray container for 100 doses is prepared. It contains:

D-Ser^1-Lys^{17,18}-β^{1-18}-corticotropin-Lys^{18}-amide	0.010 g
benzyl alcohol	0.075 g
"Miglyol" or an ester mentioned in Example 2	1.415 g
"Freon 12/114" (40:60)	6.0 g.

EXAMPLE 5

In the manner described in Examples 1 to 4, nasal sprays are prepared which contain a further 0.075 g of the ester mentioned, instead of the benzyl alcohol.

EXAMPLE 6

A solution of 10.0 mg of β^{1-24} - corticotropin stearate in 1.0 ml of absolute ethanol is mixed with 3.5 ml of "Labrafac 1219" and poured into a container with dosing valve. Then 6.5 ml of "Freon 12/114" (at the ratio of 40:60) are pressed through the valve into the container, and the "Freon" is dissolved in the alcohol+"Labrafac" mixture by agitation.

WHAT WE CLAIM IS:—

1. A pharmaceutical preparation which is suitable for resorption through the mucous membranes of the mouth or nose and contains an adrenocorticotropically active peptide in the form of a non-aqueous suspension or solution, wherein the suspending agent or solvent is selected from the group consisting of monoesters of lower alkanols having 2 to 3 carbon atoms or sorbitan-polyoxyethyleneglycol with fatty acids having 8 to 22 carbon atoms, diesters of polyoxyethyleneglycols with fatty acids having 8 to 22 carbon atoms, triesters of glycerol with fatty acids having 8 to 12 carbon atoms and mixtures of any two or more of such compounds.

2. A pharmaceutical preparation according to Claim 1 containing a liquid composition which may be administered in the form of an aerosol or spray.

3. A pharmaceutical preparation according to either of Claims 1 and 2 which contains a solution or suspension of an adrenocorticotropically active peptide in a fatty acid ester, a long-chain hydrocarbon and/or an alcohol.

4. A pharmaceutical preparation according to any one of Claims 1 to 3 which contains a solution or suspension of an adrenocorticotropically active peptide in fatty acid esters of glycerol and/or of polyoxyethylene.

5. A pharmaceutical preparation according to any one of Claims 1 to 4 which contains a solution or suspension of an adrenocorticotropically active peptide in a triglyceride mixture of fatty acids having a chain length of about 8 to 12 carbon atoms.

6. A pharmaceutical preparation according to any one of Claims 1 to 5 containing a propellant gas.

7. A pharmaceutical preparation according to any one of Claims 1 to 6 containing a halogenated hydrocarbon as propellant gas.

8. A pharmaceutical preparation according to any one of claims 1 to 7 containing fluorine and chlorine substituted methane and/or ethane as propellant gas.

9. A pharmaceutical preparation according to any one of Claims 1 to 8 containing as adrenocorticotropically active peptide a natural adrenocorticotropical hormone or a peptide having a shorter and/or different amino acid chain with respect to one or several amino acids, or a derivative, salt or complex of such peptide.

10. A pharmaceutical preparation according to any one of claims 1 to 9 containing as adrenocorticotropically active peptide D - Ser^1 - Lys^{17,18} - β^{1-18} - corticotropin - Lys^{18} - amide or a salt thereof.

11. A nasal spray containing a pharmaceutical preparation as defined in any of the preceding claims.

12. A pharmaceutical preparation substantially as described in any one of the Examples herein.

ABEL & IMRAY,
Chartered Patent Agents,
Quality House,
Quality Court,
Chancery Lane,
London W.C.2.

Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1971.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.

EXAMPLE 3

In a manner similar to that described in Example 2, a spray container for 100 doses is prepared. At contains:

D-Ser^1-Lys^{17,18}-β^{1-18}-corticotropin-Lys^{18}-amide	100 mg
benzyl alcohol	75 mg
Miglyol or an ester mentioned in Example 2	1325 mg
Freon 12/114 (40:60)	6000 mg

EXAMPLE 4

In a manner similar to that described in Example 2, a nasal spray container for 100 doses is prepared. It contains:

D-Ser^1-Lys^{17,18}-β^{1-18}-corticotropin-Lys^{18}-amide	0.010 g
benzyl alcohol	0.075 g
"Miglyol" or an ester mentioned in Example 2	1.415 g
"Freon 12/114" (40:60)	6.0 g.

EXAMPLE 5

In the manner described in Examples 1 to 4, nasal sprays are prepared which contain a further 0.075 g of the ester mentioned, instead of the benzyl alcohol.

EXAMPLE 6

A solution of 10.0 mg of β^{1-24} - cortico - tropin stearate in 1.0 ml of absolute ethanol is mixed with 3.5 ml of "Labrafac 1219" and poured into a container with dosing valve. Then 6.5 ml of "Freon 12/114" (at the ratio of 40:60) are pressed through the valve into the container, and the "Freon" is dissolved in the alcohol+"Labrafac" mixture by agitation.

WHAT WE CLAIM IS:—

1. A pharmaceutical preparation which is suitable for resorption through the mucous membranes of the mouth or nose and contains an adrenocorticotropically active peptide in the form of a non-aqueous suspension or solution, wherein the suspending agent or solvent is selected from the group consisting of monoesters of lower alkanols having 2 to 3 carbon atoms or sorbitan-polyoxyethyleneglycol with fatty acids having 8 to 22 carbon atoms, diesters of polyoxyethyleneglycols with fatty acids having 8 to 22 carbon atoms, triesters of glycerol with fatty acids having 8 to 12 carbon atoms and mixtures of any two or more of such compounds.

2. A pharmaceutical preparation according to Claim 1 containing a liquid composition which may be administered in the form of an aerosol or spray.

3. A pharmaceutical preparation according to either of Claims 1 and 2 which contains a solution or suspension of an adrenocorticotropically active peptide in a fatty acid ester, a long-chain hydrocarbon and/or an alcohol.

4. A pharmaceutical preparation according to any one of Claims 1 to 3 which contains a solution or suspension of an adrenocorticotropically active peptide in fatty acid esters of glycerol and/or of polyoxyethylene.

5. A pharmaceutical preparation according to any one of Claims 1 to 4 which contains a solution or suspension of an adrenocorticotropically active peptide in a triglyceride mixture of fatty acids having a chain length of about 8 to 12 carbon atoms.

6. A pharmaceutical preparation according to any one of Claims 1 to 5 containing a propellant gas.

7. A pharmaceutical preparation according to any one of Claims 1 to 6 containing a halogenated hydrocarbon as propellant gas.

8. A pharmaceutical preparation according to any one of claims 1 to 7 containing fluorine and chlorine substituted methane and/or ethane as propellant gas.

9. A pharmaceutical preparation according to any one of Claims 1 to 8 containing as adrenocorticotropically active peptide a natural adrenocorticotropical hormone or a peptide having a shorter and/or different amino acid chain with respect to one or several amino acids, or a derivative, salt or complex of such peptide.

10. A pharmaceutical preparation according to any one of claims 1 to 9 containing as adrenocorticotropically active peptide D - Ser^1 - Lys^{17,18} - β^{1-18} - corticotropin - Lys^{18} - amide or a salt thereof.

11. A nasal spray containing a pharmaceutical preparation as defined in any of the preceding claims.

12. A pharmaceutical preparation substantially as described in any one of the Examples herein.

ABEL & IMRAY,
Chartered Patent Agents,
Quality House,
Quality Court,
Chancery Lane,
London W.C.2.

Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1971.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.

