CLAIMS

1. A process for the preparation of an injectable sustained release pharmaceutical composition of lanreotide, comprising the steps of:

   - combining a lanreotide salt and an aqueous acetic acid solution;
   - lyophilizing the resulting mixture only once; and
   - hydrating the lyophilizate;

   wherein the final pH of the composition ranges between pH 5 to 7, and during the lyophilization step, the temperature of the mixture is

   . initially reduced from room temperature to a temperature between 1 and 5°C and then retained constant for at least one hour *(see support on page 8 line 4)*,

   . further reduced from 1 to 5°C to a temperature between -40 ± 5 °C *(see support on page 8 line 9)* and then retained constant for at least 2 hours *(see support on page 8 line 12)*,

   . initially increased for at least 10 hours from -40 ± 5 °C to 20-30 °C and then retained constant for at least 20 hours *(see support on page 8 lines 17-19)*; and

   . further increased to 30-40 °C over 1 ± 0.5 hours and then retained constant for at least 16 hours *(see support on page 8 lines 22-26)*.

2. The process of claim 1 wherein the final pH of the composition ranges between 5.8 to 6.4.

3. The process of claim 1 wherein water is used to hydrate the lyophilizate.

4. The process of claim 4 wherein water used to hydrate the lyophilizate preferably contains acid at a suitable concentration to provide the requisite final pH.

5. The process of claim 4 wherein water used to hydrate the lyophilizate contains acetic acid at a suitable concentration to provide an anhydrous acetate content of 9 ± 2 % by weight of the composition.

6. The process of claim 4 wherein water used to hydrate the lyophilizate contains acetic acid at a suitable concentration to provide an anhydrous acetate content of 9.7 ± 0.3 % by weight of the composition.

7. The process of claim 1 wherein 25 ± 2 g/l lanreotide and 15 ± 2 % by weight acetic acid are combined in the first step.

8. The process of claim 1 wherein, during the lyophilization step, the temperature of the mixture is:

- initially reduced from room temperature to 2 °C ± 1 °C and then retained constant;
- further reduced from 2 ± 1 °C to -40 ± 5 °C and then retained constant;
- initially increased from -40 ± 5 °C to 25 ± 5 °C and then retained constant; and
- further increased to 35 ± 5 °C and then retained constant.

9. The process of claim 8 wherein the duration of the lyophilization step is at least 40 hours, more preferably at least 60 hours

10. The process of claim 8 wherein, during the lyophilization step, the temperature of the mixture is:

- initially reduced over up to 30 minutes, preferably up to 10 minutes, and then retained constant for 3 ± 1 hours;
- further reduced over up to 15 minutes, preferably up to 10 minutes, and then retained constant for 3.5 ± 1 hours;
- initially increased over 20 ± 5 hours and then retained constant for at least 40 hours; and
- further increased over 1 ± 0.5 hours and then retained constant for at least 16 hours.

11. The process of claim 7 wherein, after the temperature of the mixture is decreased, the atmospheric pressure is reduced to 20 ± 5 μbar and the atmospheric pressure remains constant as the temperature of the mixture increases.

12. The process according to any of claims 1 to 10 wherein the amount of water in which the lyophilizate is dissolved is less than 50 %, preferably less than 30 %, more preferably less than 10 %, of the amount needed to completely dissolve the lanreotide salt and adapted to give the composition a semi-solid consistency.

13. The process according to any of claims 1 to 12 wherein the sustained release composition is capable of releasing the lanreotide over a period of at least 15 days, preferably 1 month, and more preferably 2 months.

14. The process according to any of claims 1 to 12 wherein the sustained release composition comprises between 15 and 35 % by weight, preferably 25 ± 5 % by weight, and more preferably approximately 24.6 ± 2.5 % by weight, of lanreotide base.

15. The process according to any of claims 1 to 12 wherein the sustained release composition is suitable for use after storage at between 2 and 8 °C for more than 12 months, preferably for more than 24 months.

CLAIMS

1. A process for the preparation of an injectable sustained release pharmaceutical composition of lanreotide, comprising the steps of:

combining a lanreotide salt and an aqueous acetic acid solution;

lyophilizing the resulting mixture only once; and

hydrating the lyophilizate;

wherein the final pH of the composition ranges between pH 5 to 7, and during the lyophilization step, the temperature of the mixture is:

initially reduced from room temperature to a temperature between 1 and 5°C and then retained constant for at least one hour,

further reduced from 1 to 5°C to a temperature between -40 ± 5°C and then retained constant for at least 2 hours,

initially increased for at least 10 hours from -40 ± 5°C to 20-30°C and then retained constant for at least 20 hours; and

further increased to 30-40°C over 1 ± 0.5 hours and then retained constant for at least 16 hours.

2. A process for the preparation of an injectable sustained release pharmaceutical composition of lanreotide, capable of releasing the lanreotide over a period of:

a) at least 15 days,

b) 1 month, or

c) 2 months

comprising the steps of:

combining a lanreotide salt and an aqueous acetic acid solution;

lyophilizing the resulting mixture only once; and

hydrating the lyophilizate;

wherein the final pH of the composition ranges between pH 5 to 7, and during the lyophilization step, the temperature of the mixture is:

initially reduced from room temperature to a temperature between 1 and 5°C and then retained constant for at least one hour,

further reduced from 1 to 5°C to a temperature between -40 ± 5°C and then retained constant for at least 2 hours,

initially increased for at least 10 hours from -40 ± 5°C to 20-30°C and then retained constant for at least 20 hours; and

further increased to 30-40°C over 1 ± 0.5 hours and then retained constant for at least 16 hours.

3. A process for the preparation of an injectable sustained release pharmaceutical composition of lanreotide, comprising between:

a) 15 and 35 % by weight,

b) 25 ± 5 % by weight, or

c) 24.6 ± 2.5 % by weight

of lanreotide base, and comprising the steps of:

combining a lanreotide salt and an aqueous acetic acid solution;

lyophilizing the resulting mixture only once; and

hydrating the lyophilizate;

wherein the final pH of the composition ranges between pH 5 to 7, and during the lyophilization step, the temperature of the mixture is:

initially reduced from room temperature to a temperature between 1 and 5°C and then retained constant for at least one hour,

further reduced from 1 to 5°C to a temperature between -40 ± 5°C and then retained constant for at least 2 hours,

initially increased for at least 10 hours from -40 ± 5°C to 20-30°C and then retained constant for at least 20 hours; and

further increased to 30-40°C over 1 ± 0.5 hours and then retained constant for at least 16 hours.

4. A process for the preparation of an injectable sustained release pharmaceutical composition of lanreotide, suitable for use after storage at between 2 and 8°C for more than 12 months, or more than 24 months comprising the steps of:

combining a lanreotide salt and an aqueous acetic acid solution;

lyophilizing the resulting mixture only once; and

hydrating the lyophilizate;

wherein the final pH of the composition ranges between pH 5 to 7, and during the lyophilization step, the temperature of the mixture is:

initially reduced from room temperature to a temperature between 1 and 5°C and then retained constant for at least one hour,

further reduced from 1 to 5°C to a temperature between -40 ± 5°C and then retained constant for at least 2 hours,

initially increased for at least 10 hours from -40 ± 5°C to 20-30°C and then retained constant for at least 20 hours; and

further increased to 30-40°C over 1 ± 0.5 hours and then retained constant for at least 16 hours.

5. The process according to any one of claims 1 to 4, wherein the final pH of the composition ranges between 5.8 to 6.4.

6. The process according to any one of claims 1 to 4, wherein water is used to hydrate the lyophilizate.

7. The process according to ~~of~~ claim 6, wherein water used to hydrate the lyophilizate contains acid at a suitable concentration to provide the requisite final pH.

8. The process according to claim 6, wherein water used to hydrate the lyophilizate contains acetic acid at a suitable concentration to provide an anhydrous acetate content of 9 ± 2 % by weight of the composition.

9. The process according to claim 6, wherein water used to hydrate the lyophilizate contains acetic acid at a suitable concentration to provide an anhydrous acetate content of 9.7 ± 0.3 % by weight of the composition.

10. The process according to any one of claims 1 to 4, wherein 25 ± 2 g/l lanreotide and 15 ± 2 % by weight acetic acid are combined in the first step.

11. The process according to any one of claims 1 to 4, wherein, during the lyophilization step, the temperature of the mixture is:

initially reduced from room temperature to 2°C ± 1°C and then retained constant;

further reduced from 2 ± 1°C to -40 ± 5°C and then retained constant;

initially increased from -40 ± 5°C to 25 ± 5°C and then retained constant; and

further increased to 35 ± 5°C and then retained constant.

12. The process according to claim 11, wherein the duration of the lyophilization step is either at least 40 hours, or at least 60 hours.

13. The process according to claim 11, wherein, during the lyophilization step, the temperature of the mixture is:

initially reduced either over up to 30 minutes, or over up to 10 minutes, and then retained constant for 3 ± 1 hours;

further reduced either over up to 15 minutes, or over up to 10 minutes, and then retained constant for 3.5 ± 1 hours;

initially increased over 20 ± 5 hours and then retained constant for at least 40 hours; and

further increased over 1 ± 0.5 hours and then retained constant for at least 16 hours.

14. The process according to claim 10, wherein, after the temperature of the mixture is decreased, the atmospheric pressure is reduced to 20 ± 5 μbar and the atmospheric pressure remains constant as the temperature of the mixture increases.

15. The process according to any one of claims 1 to 13, wherein the amount of water in which the lyophilizate is dissolved is:

a) less than 50 %,

b) less than 30 %, or

c) less than 10 %,

of the amount needed to completely dissolve the lanreotide salt and adapted to give the composition a semi-solid consistency.