METHODS FOR ADMINISTRATION AND FORMULATIONS FOR THE TREATMENT OF REGIONAL ADIPOSE TISSUE

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Appl. No. 61/181,627 filed May 27, 2009, U.S. Appl. No. 61/251,624 filed October 14, 2009, and U.S. Appl. No. 61/289,972 filed December 23, 2009.

BACKGROUND OF THE INVENTION

[0002] Excess body fat is a significant health care issue in modern societies. Chronic health conditions promoted by excess body fat include, e.g., cardiovascular disease and diabetes mellitus type 2. Moreover, excess body fat greatly undermines personal appearance and self image.

[0003] Accumulation of fat stores can occur unevenly in the body. For example, some persons may accumulate fat predominantly in visceral areas while others predominately in the subcutaneous tissue. Gender differences may also be apparent with women accumulating fat in the thighs and lateral buttocks and males in the waist. Women may accumulate fatty deposits of the thighs, which have a rumpled or "peau-de-orange" appearance, resulting in a condition referred to as cellulite. Cellulite may be related to skin architecture which allows subdermal fat herniation, sometimes referred to as adipose papillae. Other factors that may be related to cellulite include altered and/or reduced connective tissue septae, vascular and lymph changes that lead to fluid accumulation and inflammation. Fat tissue may also accumulate in the form of a fibrous fatty deposit known as a lipoma. Utilization of fat stores may occur unevenly. Persons who have lost substantial weight may still have regional pockets of fat accumulation that are resistant to reduction unless unhealthy extremes of weight loss are achieved. Exercise may affect subcutaneous fat stores differently, with deeper tissues responding with lipolysis and superficial stores being more resistant. Cellulite may also still be present despite weight loss, and lipomas are typically not affected by weight loss.

SUMMARY OF THE INVENTION

[0003a] In a first aspect, there is provided a non-sustained release formulation for use in the therapeutic treatment of regional adiposity in a human by subcutaneous injection, said formulation comprising less than or equal to 5 micrograms of an adipose tissue-reducing lipophilic long-acting selective beta-2 adrenergic receptor agonist or a salt thereof and at least one subcutaneously acceptable inactive ingredient, wherein the weekly dose is less than or equal to 5 micorgrams of said beta-2 adrenergic receptor agonist.

[0003b] In a second aspect, there is provided a non-sustained release formulation for use as defined above which comprises at least 5 nanograms of the beta-2 adrenergic receptor agonist or salt thereof.

[0003c] In a third aspect, there is provided a non-sustained release formulation for use as defined above which comprises at least 25 nanograms of the beta-2 adrenergic receptor agonist or salt thereof.

[0003d] In a fourth aspect, there is provided a non-sustained release formulation as defined above which contains 1 micrograms or less of the beta-2 adrenergic receptor agonist or salt thereof.

[0003e] In a fifth aspect, there is provided a non-sustained release formulation for use in a cosmetic fat reduction treatment in a human by subcutaneous administration wherein said non-sustained release composition comprises:

(a) a weekly dose of 5 micrograms or less of an adipose tissue-reducing lipophilic long-acting selective beta-2 adrenergic receptor agonist or a salt thereof and

(b) at least one subcutaneously acceptable inactive ingredient.

[0004] Described herein are subcutaneous and transcutaneous pharmaceutical formulations and methods of treatment using the pharmaceutical formulations for the treatment of regional adipose tissue. It has been determined that therapeutic effectiveness of a lipophilic long-acting selective beta-2 adrenergic receptor agonist and/or glucocorticosteroid, as evidenced for example by the change in circumference of a patient's waist or abdomen region, is achieved when a relatively low dose is administered to a patient. For example, in clinical trials, it is been

~~WHAT IS CLAIMED IS:~~

1. A formulation suitable for subcutaneous injection comprising:

(a) less than 20 μg of an adipose tissue-reducing lipophilic long-acting selective beta-2 adrenergic receptor agonist or a salt thereof; and

(b) at least one subcutaneously acceptable inactive ingredient.

2. The formulation of claim 1 wherein the lipophilic long-acting selective beta-2 adrenergic receptor agonist is salmeterol, formoterol, bambuterol, or a salt thereof.
3. The formulation of claim 1 wherein the lipophilic long-acting selective beta-2 adrenergic receptor agonist is salmeterol xinafoate.
4. The formulation of claim 1 wherein the formulation further comprises a glucocorticosteroid or a salt thereof.
5. The formulation of claim 4 wherein the glucocorticosteroid is in an amount of less than 25 μg.
6. The formulation of claim 5 wherein the glucocorticosteroid is dexamethasone, prednisolone, fluticasone, budesonide, or a salt thereof.
7. The formulation of claim 6 wherein the glucocorticosteroid is fluticasone or a salt thereof.
8. The formulation of claim 3 wherein the formulation provides a mean blood plasma C_{max} of salmeterol xinafoate that is equal to or less than 300 pg/mL when administered to a patient.
9. The formulation of claim 7 wherein the formulation provides a mean blood plasma C_{max} of fluticasone that is equal to or less than 100 pg/mL when administered to a patient.
10. The formulation of claim 1 wherein the lipophilic long-acting selective beta-2 adrenergic receptor agonist selectively partitions into adipose tissue relative to blood plasma when administered to a patient.
11. The formulation of claim 10 that provides a partition ratio of between 0.01 to 0.2 when the lipophilic long-acting selective beta-2 adrenergic receptor agonist is administered subcutaneously.
12. The formulation of claim 10 wherein the formulation provides a partition ratio of the lipophilic long-acting selective beta-2 adrenergic receptor agonist that is at least four times lower than the partition ratio of formoterol.

~~13. The formulation of claim 1 wherein the at least one subcutaneously acceptable inactive~~ ingredient is a co-solvent.

14. The formulation of claim 13 wherein the co-solvent is selected from polyethylene glycol and polysorbate.

15. A formulation for use in a cosmetic fat reduction treatment in a human comprising subcutaneous administration at or near the waist of the human, the formulation comprising:

(a) less than 20 μg of an adipose tissue-reducing lipophilic long-acting selective beta-2 adrenergic receptor agonist or a salt thereof; and

(b) at least one subcutaneously acceptable inactive ingredient.

16. A formulation for use in a cosmetic waist reduction treatment of at least two centimeters in a human, comprising subcutaneous administration at or near the waist of the human, the formulation comprising:

(a) less than 20 μg of an adipose tissue-reducing lipophilic long-acting selective beta-2 adrenergic receptor agonist or a salt thereof; and

(b) at least one subcutaneously acceptable inactive ingredient.

17. The formulation of claims 15 or 16 wherein the use is a weekly dose that is between 5 ng to 20 μg of the lipophilic long-acting selective beta-2 adrenergic receptor agonist.

18. The formulation of claims 15 or 16 further comprising a glucocorticosteroid in an amount that is less than 25 μg.

19. The formulation of claim 18 wherein the use is a weekly dose that is between 50 ng to ~~about~~ 25 μg of the glucocorticosteroid.

20. The formulation of claim 15 or 16 wherein the lipophilic long-acting selective beta-2 adrenergic receptor agonist is salmeterol, formoterol, bambuterol, or a salt thereof.

21. The formulation of claim 20 further comprising a glucocorticosteroid that is dexamethasone, prednisolone, fluticasone, budesonide, or a salt thereof.

22. The formulation of claim 16 wherein the two centimeter reduction in the patient's waist is evident at anytime between 4 and 8 weeks from the first day of use.

23. A formulation suitable for subcutaneous injection comprising 5 ng to 20 μg of salmeterol xinafoate and a pharmaceutically acceptable carrier therefore.

24. A formulation as claimed in claim 23 comprising 150 ng to 20 μg of salmeterol xinafoate.

25. A formulation as claimed in claim 23 comprising 300 ng to 5 μg of salmeterol xinafoate.

~~26. A formulation as claimed in claim 23 comprising 0.5 μg of salmeterol xinafoate.~~

27. A formulation as claimed in any of claims 23 to 26 which further comprises a glucocorticosteroid or salt thereof.

28. A formulation as claimed in any of claims 23 to 26 further comprising fluticasone or an ester thereof.

29. A formulation as claimed in claim 28 which comprises 5 ng to 20 μg of fluticasone propionate.

30. A formulation as claimed in claim 28 which comprises 100 ng to 5 μg of fluticasone propionate.

31. A formulation as claimed in claim 28 which comprises 0.5 μg to 2.5 μg fluticasone propionate.

32. A formulation as claimed in claim 28 which comprises 1 μg of fluticasone propionate.

33. A formulation as claimed in any of claims 23 to 32 which is an aqueous solution further containing a co-solvent.

34. A formulation as claimed in claim 32 wherein the co-solvent is polyethylene glycol or polysorbate.

35. A formulation as claimed in any of claims 23 to 34 for use in fat reduction.

36. A formulation for use as claimed in claim 35 for reduction of fat at the waist.

37. A composition as claimed in any of claims 1 to 14 which comprises at least 5 ng of the receptor agonist.

38. A composition as claimed in claim 37 which comprises at least 25 ng, or at least 50 ng, or at least 100 ng, or at least 150 ng, or at least 200 ng, or at least 300 ng of the receptor agonist.

39. A composition as claimed in claim 37 or claim 38 which contains less than 10 μg, for example less than 5 μg, such as less than 1 μg of receptor agonist.

40. A composition as claimed in any of claims 1 to 14 or 37 to 39 for use in fat reduction in a human.

41. A composition for use as claimed in claim 37 wherein the fat is fat at or near the waist.

We Claim:

1. A non-sustained release formulation for use in the therapeutic treatment of regional adiposity in a human by subcutaneous injection, said formulation comprising less than or equal to 5 micrograms of an adipose tissue-reducing lipophilic long-acting selective beta-2 adrenergic receptor agonist or a salt thereof and at least one subcutaneously acceptable inactive ingredient, wherein the weekly dose is less than or equal to 5 micorgrams of said beta-2 adrenergic receptor agonist.

2. The non-sustained release formulation for use of claim 1 wherein the amount of the beta-2 adrenergic receptor agonist or salt thereof is equal to or less than 1.0 micrograms.

3. The non-sustained release formulation for use of claim 1 wherein the lipophilic long-acting selective beta-2 adrenergic receptor agonist is salmeterol, formoterol, or a salt thereof.

4. The non-sustained release formulation for use of claim 1 wherein the lipophilic long-acting selective beta-2 adrenergic receptor agonist is salmeterol xinafoate.

5. The non-sustained release formulation for use of claim 4 wherein the amount of salmeterol xinafoate is between 5 nanograms and 5 micrograms.

6. The non-sustained release formulation for use of claim 1 wherein the formulation further comprises a glucocorticosteroid or a salt thereof.

7. The non-sustained release formulation for use of claim 6 wherein the glucocorticosteroid or salt thereof is in an amount of less than or equal to 25 micrograms.

8. The non-sustained release formulation for use of claim 6 wherein the glucocorticosteroid is dexamethasone, prednisolone, fluticasone, budesonide, or a salt thereof.

9. The non-sustained release formulation for use of claim 6 wherein the glucocorticosteroid is fluticasone or a salt thereof.

10. A non-sustained release formulation for use as claimed in any of claims 1 to 9 which comprises at least 5 nanograms of the beta-2 adrenergic receptor agonist or salt thereof.

11. A non-sustained release formulation for use as claimed in claim 10 which comprises at least 25 nanograms of the beta-2 adrenergic receptor agonist or salt thereof.

12. A non-sustained release formulation as claimed in claim 10 or claim 11 which contains 1 micrograms or less of the beta-2 adrenergic receptor agonist or salt thereof.

13. The non-sustained release formulation for use as claimed in any of claims 1 to 12 wherein the regional adiposity is at or near the waist of the human.

14. A non-sustained release formulation for use in a cosmetic fat reduction treatment in a human by subcutaneous administration wherein said non-sustained release composition comprises:

(a) a weekly dose of 5 micrograms or less of an adipose tissue-reducing lipophilic long-acting selective beta-2 adrenergic receptor agonist or a salt thereof and

(b) at least one subcutaneously acceptable inactive ingredient.

15. The formulation of claim 14 wherein the weekly dose is between 5 nanograms to 5 micrograms of the beta-2 adrenergic receptor agonist or salt thereof.

16. The formulation of claim 14 wherein the weekly dose is administered to the patient in more than one session dose.

17. The formulation of claim 16 wherein at least one session dose is administered to a patient in a sub-dose.

18. The formulation of claim 15 further comprising a glucocorticosteroid or a salt thereof is present in an amount that is less than or equal to 25 micrograms.

19. The formulation of claim 18 wherein a weekly dose of between 50 nanograms to 25 micrograms of the glucocorticosteroid or salt thereof is administered to the human.

20. The formulation of claim 14 wherein the lipophilic long-acting selective beta-2 adrenergic receptor agonist is salmeterol, formoterol, or a salt thereof.

21. The formulation of claim 20 further comprising a glucocorticosteroid that is dexamethasone, prednisolone, fluticasone, budesonide, or a salt thereof.

22. The formulation for the use of claim 1 comprising 5 nanograms to 5 micrograms of salmeterol xinafoate and a pharmaceutically acceptable carrier.

23. The formulation for use of claim 22 comprising 150 nanograms to 5 micrograms of salmeterol xinafoate.

24. The formulation for use of claim 23 comprising 300 nanograms to 5 micrograms of salmeterol xinafoate.

25. The formulation for use of claim 24 comprising 0.5 micrograms of salmeterol xinafoate.

26. The formulation for use of any of claims 22 to 25 which further comprises a glucocorticosteroid or a salt thereof.

27. The formulation for use of any of claims 22 to 25 further comprising fluticasone or a salt thereof.

28. The formulation for use of claim 27 which comprises 5 nanograms to 20 micrograms of fluticasone propionate.

29. The formulation for use of claim 28 which comprises 100 nanograms to 5 micrograms of fluticasone propionate.

30. The formulation for use of claim 28 which comprises 0.5 micrograms to 2.5 micrograms of fluticasone propionate.

31. The formulation for use of claim 28 which comprises 1 micrograms of fluticasone propionate.

32. The formulation for use of any of claims 22 to 31 which is an aqueous solution further containing at least one co-solvent.

33. The formulation for use of claim 32 wherein the co-solvent is polyethylene glycol or polysorbate.