CLAIMS:

1. A composition, comprising a hyaluronidase for use in the treatment of diabetes in combination with continuous subcutaneous insulin infusion (CSII) therapy of an insulin composition, wherein:

the composition comprising the hyaluronidase is formulated for administration separately from the CSII therapy for administration prior to infusion of an insulin composition by CSII; and

the composition comprising the hyaluronidase is formulated for direct administration in an amount that minimizes changes in insulin absorption that occurs over a course of continuous subcutaneous insulin infusion (CSII).

2. Use of a composition comprising a hyaluronidase for manufacture of a medicament for treatment of diabetes in combination with continuous subcutaneous insulin infusion (CSII) therapy of an insulin composition, wherein:

the composition comprising the hyaluronan-degrading enzyme is formulated for administration separately from insulin in the CSII therapy for administration prior to infusion of the insulin composition by CSII; and

the composition comprising the hyaluronan-degrading enzyme is formulated for direct administration in an amount that minimizes changes in insulin absorption that occurs over a course of continuous subcutaneous insulin infusion (CSII).

3. The composition of claim 1, wherein the hyaluronidase is in a therapeutically effective amount sufficient to catalyze the hydrolysis of hyaluronic acid to increase tissue permeability.

4. The composition of claim 1 or claim 3, wherein the hyaluronidase is active at neutral pH.

5. The composition of any of claims 1, 3 or 4, wherein:

the hyaluronidase lacks a glycosylphosphatidylinositol (GPI) anchor or is not membrane-associated when expressed from a cell; or

the hyaluronidase contains C-terminal truncations of one or more amino acid residues and lacks all or part of a GPI anchor.

6. The composition of any of claims 1 or 3 -5, wherein the hyaluronidase is a PH20 or a C-terminally truncated fragment thereof.

7. The composition of any of claims 1 or 3-6, wherein the hyaluronidase is a PH20 polypeptide that has the sequence of amino acids set forth in any of SEQ ID NOS: 4-9, 47-48, 234-254, and 267-273, or a sequence of amino acids that exhibits at least 85% sequence identity to any of SEQ ID NOS: 4-9, 47-48, 234-254, and 267-273 and retains hyaluronidase activity.

8. The composition of any of claims 1 or 3-7, wherein the hyaluronidase is a C-terminal truncated PH20 that comprises the sequence of amino set forth in any of SEQ ID NOS: 4-9, or a sequence of amino acids that exhibits at least 85% sequence identity to the sequence of amino acids set forth in any one of SEQ ID NOS:4-9 and retains hyaluronidase activity.

9. The composition of claim 7, wherein the PH20 has the sequence of amino acids set forth in any one of SEQ ID NOS:4-9.

10. The composition of any of claims 1 or 3-9, wherein:

the hyaluronidase in the composition is in an amount that is functionally equivalent to between or about between 1 Unit to 200 Units, 5 Units to 150 Units, 10 Units to 150 Units, 50 Units to 150 Units or 1 Unit to 50 Units; or

the hyaluronidase in the composition is in an amount that is between or about between 8 ng to 2 μg, 20 ng to 1.6 μg, 80 ng to 1.25 μg or 200 ng to 1 μg.

11. The composition of any of claims 1 or 3-10, wherein the hyaluronidase in the composition is in an amount between or about between 10 Units/mL to 20,000 Units/mL, 30 Units/mL to 3000 U/mL, 100 U/mL to 1000 U/mL, 300 U/mL to 2000 U/mL, 600 U/mL to 2000 U/mL or 600 U/mL to 1000 U/mL.

12. The composition of any of claims 1 or 3-11, wherein the insulin composition for use in continuous subcutaneous insulin infusion (CSII) therapy comprises a fast-acting insulin.

13. The composition of claim 12, wherein the fast-acting insulin is a regular insulin.

14. The composition of claim 13, wherein the regular insulin is a human insulin or pig insulin.

15. The composition of claim 13 or claim 14, wherein the regular insulin is an insulin with an A chain having the sequence of amino acids set forth in SEQ ID NO:103 and a B chain having the sequence of amino acids set forth in SEQ ID NO:104 or an insulin with an A chain with the sequence of amino acids set forth as amino acid residue positions 88-108 of SEQ ID NO:123 and a B chain with the sequence of amino acids set forth as amino acid residue positions 25-54 of SEQ ID NO:123.

16. The composition of claim 12, wherein the fast-acting insulin is a fast-acting insulin analog.

17. The composition of claim 16, wherein the fast-acting insulin analog is insulin aspart, insulin lispro or insulin glulisine.

18. The composition of claim 17, wherein the fast-acting insulin analog is selected from among an insulin having an A chain with the sequence of amino acids set forth in SEQ NOS:103 and a B chain having the sequence of amino acids set forth in any of SEQ NOS:147-149.

19. The composition of any of claims 12-18, wherein the fast-acting insulin is formulated in the insulin composition for CSII in an amount that is from or from about 100 U/mL to 1000 U/mL or 500 U/mL to 1000 U/mL.

20. The composition of any of claims 1 or 3-19, wherein the composition comprising the hyaluronidase is formulated for use 15 seconds to 1 hour, 30 seconds to 30 minutes, 1 minute to 15 minutes, 1 minute to 12 hours, 5 minutes to 6 hours, 30 minutes to 3 hours, or 1 hour to 2 hours prior to infusion of the insulin composition by CSII.

21. The composition of any of claims 1 or 3-20, wherein the composition comprising the hyaluronidase is formulated for use no more than 2 hours before infusion of the insulin composition by CSII.

22. The use of claim 2, wherein the hyaluronidase is in a therapeutically effective amount sufficient to catalyze the hydrolysis of hyaluronic acid to increase tissue permeability.

23. The use of claim 2 or claim 22, wherein the hyaluronidase is active at neutral pH.

24. The use of any of claims 2, 22 or 23, wherein:

the hyaluronidase lacks a glycosylphosphatidylinositol (GPI) anchor or is not membrane-associated when expressed from a cell; or

the hyaluronidase contains C-terminal truncations of one or more amino acid residues and lacks all or part of a GPI anchor.

25. The use of any of claims 2 or 22-24, wherein the hyaluronidase is a PH20 or a C-terminally truncated fragment thereof.

26. The use of any of claims 2 or 22-25, wherein the hyaluronidase is a PH20 polypeptide that has the sequence of amino acids set forth in any of SEQ ID NOS: 4-9, 47-48, 234-254, and 267-273, or a sequence of amino acids that exhibits at least 85% sequence identity to any of SEQ ID NOS: 4-9, 47-48, 234-254, and 267-273 and retains hyaluronidase activity.

27. The use of any of claim 2 or 22-26, wherein the hyaluronidase is a C-terminal truncated PH20 that comprises the sequence of amino set forth in any of SEQ ID NOS: 4-9, or a sequence of amino acids that exhibits at least 85% sequence identity to the sequence of amino acids set forth in any one of SEQ ID NOS:4-9 and retains hyaluronidase activity.

28. The use of claim 26, wherein the PH20 has the sequence of amino acids set forth in any one of SEQ ID NOS:4-9.

29. The use of any of claims 2 or 22-28, wherein:

the hyaluronidase in the composition is in an amount that is functionally equivalent to between or about between 1 Unit to 200 Units, 5 Units to 150 Units, 10 Units to 150 Units, 50 Units to 150 Units or 1 Unit to 50 Units; or

the hyaluronidase in the composition is in an amount that is between or about between 8 ng to 2 μg, 20 ng to 1.6 μg, 80 ng to 1.25 μg or 200 ng to 1 μg.

30. The use of any of claims 2 or 22-29, wherein the hyaluronidase in the composition is in an amount between or about between 10 Units/mL to 20,000 Units/mL, 30 Units/mL to 3000 U/mL, 100 U/mL to 1000 U/mL, 300 U/mL to 2000 U/mL, 600 U/mL to 2000 U/mL or 600 U/mL to 1000 U/mL.

31. The use of any of claims 2 or 22-30, wherein the insulin composition for use in continuous subcutaneous insulin infusion (CSII) therapy comprises a fast-acting insulin.

32. The use of claim 31, wherein the fast-acting insulin is a regular insulin.

33. The use of claim 32, wherein the regular insulin is a human insulin or pig insulin.

34. The use of claim 33, wherein the regular insulin is an insulin with an A chain having the sequence of amino acids set forth in SEQ ID NO:103 and a B chain having the sequence of amino acids set forth in SEQ ID NO:104 or an insulin with an A chain with the sequence of amino acids set forth as amino acid residue positions 88-108 of SEQ ID NO:123 and a B chain with the sequence of amino acids set forth as amino acid residue positions 25-54 of SEQ ID NO:123.

35. The use of claim 31, wherein the fast-acting insulin is an insulin analog.

36. The use of claim 35, wherein the fast-acting insulin analog is insulin aspart, insulin lispro or insulin glulisine.

37. The use of claim 36, wherein the fast-acting insulin analog is selected from among an insulin having an A chain with the sequence of amino acids set forth in SEQ NOS:103 and a B chain having the sequence of amino acids set forth in any of SEQ NOS:147-149.

38. The use of any of claims 31-37, wherein the fast-acting insulin is formulated in the insulin composition for CSII in an amount that is from or from about 100 U/mL to 1000 U/mL or 500 U/mL to 1000 U/mL.

39. The use of any of claims 2 or 22-38, wherein the composition comprising the hyaluronidase is formulated for use 15 seconds to 1 hour, 30 seconds to 30 minutes, 1 minute to 15 minutes, 1 minute to 12 hours, 5 minutes to 6 hours, 30 minutes to 3 hours, or 1 hour to 2 hours prior to infusion of the insulin composition by CSII.

40. The use of any of claims 2 or 22-39, wherein the composition comprising the hyaluronidase is formulated for use no more than 2 hours before infusion of the insulin composition by CSII.

CLAIMS:

1. A composition, comprising a hyaluronidase for use in the treatment of diabetes in combination with continuous subcutaneous insulin infusion (CSII) therapy of an insulin composition, wherein:

the composition comprising the hyaluronidase is formulated for administration separately from the CSII therapy for administration prior to infusion of an insulin composition by CSII; and

the composition comprising the hyaluronidase is formulated for direct administration in an amount that minimizes changes in insulin absorption that occurs over a course of continuous subcutaneous insulin infusion (CSII).

2. Use of a composition comprising a hyaluronidase for manufacture of a medicament for treatment of diabetes in combination with continuous subcutaneous insulin infusion (CSII) therapy of an insulin composition, wherein:

the composition comprising the hyaluronan-degrading enzyme is formulated for administration separately from insulin in the CSII therapy for administration prior to infusion of the insulin composition by CSII; and

the composition comprising the hyaluronan-degrading enzyme is formulated for direct administration in an amount that minimizes changes in insulin absorption that occurs over a course of continuous subcutaneous insulin infusion (CSII).

3. The composition or use of claim 1 or claim 2, wherein the hyaluronidase is in a therapeutically effective amount sufficient to catalyze the hydrolysis of hyaluronic acid to increase tissue permeability.

4. The composition or use of any of claims 1-3, wherein the hyaluronidase is active at neutral pH.

5. The composition or use of any of claims 1-4, wherein:

the hyaluronidase lacks a glycosylphosphatidylinositol (GPI) anchor or is not membrane-associated when expressed from a cell; or

the hyaluronidase contains C-terminal truncations of one or more amino acid residues and lacks all or part of a GPI anchor.

6. The composition or use of any of claims 1-5, wherein the hyaluronidase is a PH20 or a C-terminally truncated fragment thereof.

7. The composition or use of any of claims 1-6, wherein the hyaluronidase is a PH20 polypeptide that has the sequence of amino acids set forth in any of SEQ ID NOS: 4-9, 47-48, 234-254, and 267-273, or a sequence of amino acids that exhibits at least 85% sequence identity to any of SEQ ID NOS: 4-9, 47-48, 234-254, and 267-273 and retains hyaluronidase activity.

8. The composition or use of any of claims 1-7, wherein the hyaluronidase is a C-terminal truncated PH20 that comprises the sequence of amino set forth in any of SEQ ID NOS: 4-9, or a sequence of amino acids that exhibits at least 85% sequence identity to the sequence of amino acids set forth in any one of SEQ ID NOS:4-9 and retains hyaluronidase activity.

9. The composition or use of any of claims 1-8, wherein the PH20 has the sequence of amino acids set forth in any one of SEQ ID NOS:4-9.

10. The composition or use of any of claims 1-9, wherein:

the hyaluronidase in the composition is in an amount that is functionally equivalent to between or about between 1 Unit to 200 Units, 5 Units to 150 Units, 10 Units to 150 Units, 50 Units to 150 Units or 1 Unit to 50 Units; or

the hyaluronidase in the composition is in an amount that is between or about between 8 ng to 2 µg, 20 ng to 1.6 µg, 80 ng to 1.25 µg or 200 ng to 1 µg.

11. The composition or use of any of claims 1-10, wherein the hyaluronidase in the composition is in an amount between or about between 10 Units/mL to 20,000 Units/mL, 30 Units/mL to 3000 U/mL, 100 U/mL to 1000 U/mL, 300 U/mL to 2000 U/mL, 600 U/mL to 2000 U/mL or 600 U/mL to 1000 U/mL.

12. The composition or use of any of claims 1-11, wherein the insulin composition for use in continuous subcutaneous insulin infusion (CSII) therapy comprises a fast-acting insulin.

13. The composition or use of claim 12, wherein the fast-acting insulin is a regular insulin.

14. The composition or use of claim 13, wherein the regular insulin is a human insulin or pig insulin.

15. The composition or use of claim 13 or claim 14, wherein the regular insulin is an insulin with an A chain having the sequence of amino acids set forth in SEQ ID NO:103 and a B chain having the sequence of amino acids set forth in SEQ ID NO:104 or an insulin with an A chain with the sequence of amino acids set forth as amino acid residue positions 88-108 of SEQ ID NO:123 and a B chain with the sequence of amino acids set forth as amino acid residue positions 25-54 of SEQ ID NO:123.

16. The composition or use of claim 12, wherein the fast-acting insulin is an insulin analog.

17. The composition or use of claim 16, wherein the fast-acting insulin analog is insulin aspart, insulin lispro or insulin glulisine.

18. The composition or use of claim 17, wherein the insulin analog is selected from among an insulin having an A chain with the sequence of amino acids set forth in SEQ NOS:103 and a B chain having the sequence of amino acids set forth in any of SEQ NOS:147-149.

19. The composition or use of any of claims 12-18, wherein the fast-acting insulin is formulated in the insulin composition for CSII in an amount that is from or from about 100 u/mL to 1000 U/mL or 500 U/mL to 1000 U/mL.

20. The composition or use of any of claims 1-19, wherein the composition comprising the hyaluronidase is formulated for use 15 seconds to 1 hour, 30 seconds to 30 minutes, 1 minute to 15 minutes, 1 minute to 12 hours, 5 minutes to 6 hours, 30 minutes to 3 hours, or 1 hour to 2 hours prior to infusion of the insulin composition by CSII.

21. The composition or use of any of claims 1-20, wherein the composition comprising the hyaluronidase is formulated for use no more than 2 hours before infusion of the insulin composition by CSII.