WHAT IS CLAIMED IS:

1. An aqueous pharmaceutical composition comprising etanercept and a stabilizer to inhibit instability, aggregation, misfolding and/or fragmentation of the etanercept, wherein the stabilizer comprises a stabilizing metal ion.

2. The composition of claim 1 wherein a source of said stabilizing metal ion is selected from the group consisting of calcium, magnesium and zinc.

3. The composition of claim 2, further comprising one or more additional components selected from: a buffer; a tonicity modifier, and an excipient.

4. The metal ion stabilized etanercept composition of claim 3 where the stabilizer is calcium chloride, the formulation is free or essentially free of arginine, and the formulation elicits long term storage stability as characterized by at least one of:

   SEC analysis at M_3 or T_2 or T_4 of: monomer content greater than about 90 wt.%; aggregates content of less than about 3 wt.%; and fragment 3 content less than about 5 wt%; and

   HIC analysis at M_3 or T_2 or T_4 wherein the amount of the composition represented by peak 1 of the HIC chromatogram is less than about 3 wt.%; the amount of the composition represented by peak 2 of the HIC chromatogram is greater than 80 wt.%; and the amount of the composition represented by peak 3 of the HIC chromatogram is less than about 20 wt.%.

5. The metal ion stabilized etanercept composition of claim 3 wherein the stabilizer is calcium chloride in an amount not exceeding about 5 mM calcium chloride; optionally about 0.5 to 6 wt.% sucrose or trehalose; optionally about 0 to100 mM NaCl; optionally up to about 10 mM xylitol; about 1 to about 30 mM sodium phosphate; wherein the composition has a pH of about 6.0 to 6.6; and wherein, optionally, the composition contains no arginine or is essentially free of arginine.

6. The calcium chloride stabilized composition of claim 5 eliciting long term storage stability as characterized by:

SEC analysis M_3 or T_2 or T_4 of greater than about 90 wt.% monomer content; less than about 3 wt.% aggregate(s) content; and less than about 5 wt% fragment 3; and

HIC analysis at M_3 or T_2 or T_4 wherein the amount of the composition represented by peak 1 of the HIC chromatogram is less than about 3 wt.%; the amount of the composition represented by peak 2 of the HIC chromatogram is greater than 80 wt.%; and the amount of the composition represented by peak 3 of the HIC chromatogram is less than about 20 wt.%.

7. The calcium chloride stabilized composition of claim 6 eliciting long term storage stability as characterized by: an HIC analysis at M_3 wherein the amount of the composition represented by peak 2 of the HIC chromatogram is greater than or equal to about 95 wt.%; and wherein, if peak 3 is present on the HIC chromatogram, the amount of the composition represented by peak 3 is less than or equal to about 3 wt.%.

8. The calcium chloride stabilized composition of claim 6 having, at M_3 or T_2 or T_4 no more than, on average, about 10,000 subvisible particles per mL having a size greater than 5μm.

9. The calcium chloride stabilized composition of claim 6 comprising about 50 mg/ml of etanercept; about 2 mM calcium chloride; less than about 30 mM sodium phosphate; less than about 150 mM sodium chloride; and less than about 4 wt.% sucrose; wherein the formulation has a pH of about 6.3 to 6.5.

10. The calcium chloride stabilized composition of claim 6 comprising about 50 mg/ml of etanercept; about 2 mM calcium chloride; about 10-30 mM sodium phosphate; less than about 10 wt.% sucrose; wherein the formulation has a pH of about 6.3 to 6.5.

11. The calcium chloride stabilized composition of claim 6 comprising about 50 mg/ml of etanercept; about 2 mM calcium chloride; about 10-30 mM sodium phosphate; less than about 100 mM sodium chloride; less than about 5 wt.% sucrose; wherein the formulation has a pH of about 6.3 to 6.5.

12. The calcium chloride stabilized composition of claim 6 comprising about 50 mg/ml of etanercept; about 1 mM calcium chloride; about 10-30 mM sodium phosphate; about 25 to about 75 mM sodium chloride; and less than about 8 wt.% trehalose; wherein the formulation has a pH of about 6.3 to 6.5.

13. The stabilized etanercept composition of claim 3 where the stabilizer is magnesium chloride, the formulation is free or essentially free of arginine, and the formulation elicits long term storage stability as characterized by at least one of:

SEC analysis at M_3 or T_2 or T_4 of: monomer content greater than about 90%; aggregates content of less than about 3 wt%; and fragment 3 content less than about 5 wt%: and

HIC analysis at M_3 or T_2, or T_4 wherein the amount of the composition represented by peak 1 of the HIC chromatogram is less than about 3 wt.%; the amount of the composition represented by peak 2 of the HIC chromatogram is greater than 80 wt.%; and the amount of the composition represented by peak 3 of the HIC chromatogram is less than about 20 wt.%.

14. The stabilized etanercept composition of claim 3 wherein the stabilizer is magnesium chloride and the formulation comprises comprising about 1 mM to about 20 mM magnesium chloride; optionally up to about 6 wt.% sucrose; about 25 to 150 mM NaCl; about 1 to about 30 mM sodium phosphate; wherein the composition has a pH of about 6.0 to 6.6; and wherein, optionally, the composition contains no arginine or is essentially free of arginine.

15. The magnesium chloride stabilized composition of claim 14 eliciting long term storage stability as characterized by:

SEC analysis at M_3 or T_2, or T_4 of greater than about 90 wt.% monomer content; less than about 3 wt.% aggregate(s) content; and less than about 5 wt% fragment 3; and

(b) an HIC analysis at M_3 or T_2 or T_4 wherein the amount of the composition represented by peak 1 of the HIC chromatogram is less than about 3 wt.%; the amount of the composition represented by peak 2 of the HIC chromatogram is greater than 80 wt.%; and the amount of the composition represented by peak 3 of the HIC chromatogram is less than about 20 wt.%; and

16. The magnesium chloride stabilized composition of claim 15 which elicits long term storage stability as characterized by: an HIC analysis at M_3 or T_2 or T_4 wherein the amount of the composition represented by peak 2 of the HIC chromatogram is greater than or equal to about 95 wt.%; and wherein, if peak 3 is present on the HIC chromatogram, the amount of the composition represented by peak 3 is less than or equal to about 3 wt.%.

17. The magnesium chloride stabilized composition of claim 15 having, on average, no more than about 10,000 subvisible particles per mL having a size greater than 5μm.

18. The magnesium chloride stabilized composition of claim 15 comprising about 50 mg/ml of etanercept; about 10 mM magnesium chloride; about 10-30 mM sodium phosphate; less than about 150 mM sodium chloride; and less than about 3 wt.% sucrose; and having a pH of about 6.3 to 6.5.

19. The magnesium chloride stabilized composition of claim 15 comprising about 50 mg/ml of etanercept; about 5 mM magnesium chloride; less than about 30 mM sodium phosphate; less than about 100 mM sodium chloride; and less than about 4 wt.% sucrose; and having a pH of about 6.3 to 6.5.

20. The magnesium chloride stabilized composition of claim 15 comprising about 50 mg/ml of etanercept; about 4 mM magnesium chloride; less than about 30 mM sodium phosphate; about 100 mM sodium chloride; and about 2.5 wt.% sucrose; and having a pH of about 6.3 to 6.5.

21. The magnesium chloride stabilized composition of claim 15 comprising about 50 mg/ml of etanercept; about 10 mM magnesium chloride; less than about 30 mM sodium phosphate; less than about 100 mM sodium chloride; and less than about 5 wt.% sucrose; and having a pH of about 6.3 to 6.5.

22. The stabilized etanercept composition of claim 1, containing no arginine, or essentially free of arginine, wherein the composition, at M_3 or T_2 or T_4 elicits long term storage stability that meets one or both of the following criteria:

(A) stability comparable to or better than commercially available etanercept marketed under the trademark Enbrel®, as measured by (i) SEC analysis of the amounts of aggregate(s), monomer and fragment 3 in the composition (as defined in the specification) and (ii) HIC analysis of amounts of material in the composition corresponding to peaks 1, 2 and 3 of the HIC chromatogram (as defined in the specification); and

(B) an HIC chromatogram in which (i) peak 3 is absent, or essentially absent and (ii) peak 2 represents greater than about 95 wt% of the composition; an SEC chromatogram containing essentially no peak corresponding to aggregate(s); and an SEC chromatogram in which the monomer content represents at least about 95 wt% of the composition.

WHAT IS CLAIMED IS:

1. An aqueous pharmaceutical composition comprising etanercept and a stabilizer to inhibit instability, aggregation, misfolding and/or fragmentation of the etanercept, wherein the stabilizer comprises a stabilizing metal ion.

2. The composition of claim 1 wherein a source of said stabilizing metal ion is selected from the group consisting of calcium, magnesium and zinc.

3. The composition of claim 2, further comprising one or more additional components selected from: a buffer; a tonicity modifier, and an excipient.

4. The metal ion stabilized etanercept composition of claim 3 where the stabilizer is calcium chloride, the formulation is free or essentially free of arginine, and the formulation elicits long term storage stability as characterized by at least one of:

   SEC analysis at M_3 or T_2 or T_4 of: monomer content greater than 90 wt.%; aggregates content of less than 3 wt.%; and fragment 3 content less than 5 wt%: and

   HIC analysis at M_3 or T_2 or T_4 wherein the amount of the composition represented by peak 1 of the HIC chromatogram is less than 3 wt.%; the amount of the composition represented by peak 2 of the HIC chromatogram is greater than 80 wt.%; and the amount of the composition represented by peak 3 of the HIC chromatogram is less than 20 wt.%.

5. The metal ion stabilized etanercept composition of claim 3 wherein the stabilizer is calcium chloride in an amount not exceeding 5 mM calcium chloride; optionally 0.5 to 6 wt.% sucrose or trehalose; optionally 0 to100 mM NaCl; optionally up to 10 mM xylitol; 1 to 30 mM sodium phosphate; wherein the composition has a pH of 6.0 to 6.6; and wherein, optionally, the composition contains no arginine or is essentially free of arginine.

6. The calcium chloride stabilized composition of claim 5 eliciting long term storage stability as characterized by:

SEC analysis M_3 or T_2 or T_4 of greater than 90 wt.% monomer content; less than 3 wt.% aggregate(s) content; and less than 5 wt% fragment 3; and

HIC analysis at M_3 or T_2 or T_4 wherein the amount of the composition represented by peak 1 of the HIC chromatogram is less than 3 wt.%; the amount of the composition represented by peak 2 of the HIC chromatogram is greater than 80 wt.%; and the amount of the composition represented by peak 3 of the HIC chromatogram is less than 20 wt.%.

7. The calcium chloride stabilized composition of claim 6 eliciting long term storage stability as characterized by: an HIC analysis at M_3 wherein the amount of the composition represented by peak 2 of the HIC chromatogram is greater than or equal to 95 wt.%; and wherein, if peak 3 is present on the HIC chromatogram, the amount of the composition represented by peak 3 is less than or equal to 3 wt.%.

8. The calcium chloride stabilized composition of claim 6 having, at M_3 or T_2 or T_4 no more than, on average, 10,000 subvisible particles per mL having a size greater than 5µm.

9. The calcium chloride stabilized composition of claim 6 comprising about 50 mg/ml of etanercept; about 2 mM calcium chloride; less than 30 mM sodium phosphate; less than 150 mM sodium chloride; and less than 4 wt.% sucrose; wherein the formulation has a pH of 6.3 to 6.5.

10. The calcium chloride stabilized composition of claim 6 comprising about 50 mg/ml of etanercept; about 2 mM calcium chloride; 10-30 mM sodium phosphate; less than 10 wt.% sucrose; wherein the formulation has a pH of 6.3 to 6.5.

11. The calcium chloride stabilized composition of claim 6 comprising about 50 mg/ml of etanercept; about 2 mM calcium chloride; 10-30 mM sodium phosphate; less than 100 mM sodium chloride; less than 5 wt.% sucrose; wherein the formulation has a pH of 6.3 to 6.5.

12. The calcium chloride stabilized composition of claim 6 comprising about 50 mg/ml of etanercept; about 1 mM calcium chloride; 10-30 mM sodium phosphate; 25 to 75 mM sodium chloride; and less than 8 wt.% trehalose; wherein the formulation has a pH of 6.3 to 6.5.

13. The stabilized etanercept composition of claim 3 where the stabilizer is magnesium chloride, the formulation is free or essentially free of arginine, and the formulation elicits long term storage stability as characterized by at least one of:

SEC analysis at M_3 or T_2 or T_4 of: monomer content greater than 90%; aggregates content of less than 3 wt%; and fragment 3 content less than 5 wt%: and

HIC analysis at M_3 or T_2, or T_4 wherein the amount of the composition represented by peak 1 of the HIC chromatogram is less than 3 wt.%; the amount of the composition represented by peak 2 of the HIC chromatogram is greater than 80 wt.%; and the amount of the composition represented by peak 3 of the HIC chromatogram is less than 20 wt.%.

14. The stabilized etanercept composition of claim 3 wherein the stabilizer is magnesium chloride and the formulation comprises comprising 1 mM to 20 mM magnesium chloride; optionally up to 6 wt.% sucrose; 25 to 150 mM NaCl; 1 to 30 mM sodium phosphate; wherein the composition has a pH of 6.0 to 6.6; and wherein, optionally, the composition contains no arginine or is essentially free of arginine.

15. The magnesium chloride stabilized composition of claim 14 eliciting long term storage stability as characterized by:

SEC analysis at M_3 or T_2, or T_4 of greater than 90 wt.% monomer content; less than 3 wt.% aggregate(s) content; and less than 5 wt% fragment 3; and

(b) an HIC analysis at M_3 or T_2 or T_4 wherein the amount of the composition represented by peak 1 of the HIC chromatogram is less than

3 wt.%; the amount of the composition represented by peak 2 of the HIC chromatogram is greater than 80 wt.%; and the amount of the composition represented by peak 3 of the HIC chromatogram is less than 20 wt.%.

16. The magnesium chloride stabilized composition of claim 15 which elicits long term storage stability as characterized by: an HIC analysis at M_3 or T_2 or T_4 wherein the amount of the composition represented by peak 2 of the HIC chromatogram is greater than or equal to 95 wt.%; and wherein, if peak 3 is present on the HIC chromatogram, the amount of the composition represented by peak 3 is less than or equal to 3 wt.%.

17. The magnesium chloride stabilized composition of claim 15 having, on average, no more than 10,000 subvisible particles per mL having a size greater than 5μm.

18. The magnesium chloride stabilized composition of claim 15 comprising about 50 mg/ml of etanercept; about 10 mM magnesium chloride; 10-30 mM sodium phosphate; less than 150 mM sodium chloride; and less than 3 wt.% sucrose; and having a pH of 6.3 to 6.5.

19. The magnesium chloride stabilized composition of claim 15 comprising about 50 mg/ml of etanercept; about 5 mM magnesium chloride; less than 30 mM sodium phosphate; less than 100 mM sodium chloride; and less than 4 wt.% sucrose; and having a pH of 6.3 to 6.5.

20. The magnesium chloride stabilized composition of claim 15 comprising about 50 mg/ml of etanercept; about 4 mM magnesium chloride; less than 30 mM sodium phosphate; about 100 mM sodium chloride; and about 2.5 wt.% sucrose; and having a pH of 6.3 to 6.5.

21. The magnesium chloride stabilized composition of claim 15 comprising about 50 mg/ml of etanercept; about 10 mM magnesium chloride; less than 30 mM sodium phosphate; less than 100 mM sodium chloride; and less than 5 wt.% sucrose; and having a pH of 6.3 to 6.5.

22. The stabilized etanercept composition of claim 1, containing no arginine, or essentially free of arginine, wherein the composition, at M_3 or T_2 or T_4 elicits long term storage stability that meets one or both of the following criteria:

(A) stability comparable to or better than commercially available etanercept marketed under the trademark Enbrel®, as measured by (i) SEC analysis of the amounts of aggregate(s), monomer and fragment 3 in the composition (as defined in the specification) and (ii) HIC analysis of amounts of material in the composition corresponding to peaks 1, 2 and 3 of the HIC chromatogram (as defined in the specification); and

(B) an HIC chromatogram in which (i) peak 3 is absent, or essentially absent and (ii) peak 2 represents greater than 95 wt% of the composition; an SEC chromatogram containing essentially no peak corresponding to aggregate(s); and an SEC chromatogram in which the monomer content represents at least 95 wt% of the composition.