CLAIMS

What is claimed is:

1. ~~A method of~~Use of methotrexate (MTX) and a PEGylated uricase in the manufacture of a medicament for treating gout in a patient having a serum uric acid (SUA) level of ≥ 6 mg/dL ~~comprising~~, wherein:

~~administering methotrexate (~~MTX~~)~~ is to be administered to said patient at a single dose of about 15 mg per week for a period of 2 to 4 weeks prior to a first administration of ~~a PEGylated uricase; and~~

~~co-administering~~ the PEGylated uricase; and ~~MTX~~

the PEGylated uricase and MTX are to be co-administered to said patient using a dosage regimen comprising a dose of about 8 mg to about 32 mg of the PEGylated uricase intravenously every 2 to 4 weeks ~~for a total of 6 to 26 doses~~, and a dose of about 15 mg of MTX per week~~,~~ ~~wherein the co-administered MTX is administered concurrently with each administration of the PEGylated uricase~~;

wherein the PEGylated uricase is to be administered over an infusion period of 60 minutes or less; and

wherein the infusion volume is about 50 mL.

2. ~~A method of~~Use of a PEGylated uricase and methotrexate (MTX) in the manufacture of a medicament for reducing immunogenicity to PEGylated uricase and prolonging the urate lowering effect ~~comprising~~ , wherein the PEGylated uricase and MTX are to be co-~~administering a PEGylated uricase at~~administered using a dosage regimen comprising a dosage of about 8 mg to about 32 mg of the PEGylated uricase intravenously every 2 to 4 weeks, and ~~methotrexate (MTX) at~~ a single dosage of about 15 mg of MTX per week to a patient having a serum uric acid (SUA) level of ≥ 6 mg/dL prior to PEGylated uricase treatment initiation,

wherein the administration of the PEGylated uricase and MTX result in the SUA level being reduced relative to a patient not receiving co-administration of the PEGylated uricase and MTX immunosuppressive therapy,

wherein the PEGylated uricase is to be administered over an infusion period of 60 minutes or less; and

wherein the infusion volume is about 50 mL.

3. The ~~method~~use of claims 1 or 2, wherein the infusion period is 45 minutes and the infusion volume is 50 mL.

4. The ~~method~~use of any of claims 1 to 3, wherein the infusion period is 30 minutes.

5. The ~~method~~use of any of claims 1 to 4, wherein the patient lacks one or more of the following symptoms:

(i) respiratory symptoms: difficulty breathing with wheezing or stridor; upper airway swelling (lip, tongue, throat, uvula, or larynx); respiratory distress manifested as at least 2 or more of the following: tachypnoea, increased use of accessory respiratory muscles, cyanosis, recession, grunting; or

(ii) cardiovascular symptoms: hypertension, tachycardia, measured hypotension, a decreased level of consciousness, loss of consciousness; or

(iii) dermatological or mucosal symptoms: generalized urticaria (hives) or generalized erythema, angioedema, generalized pruritus with skin rash.

6. The ~~method~~use of any of claims 1 to 5, wherein patients:

(i) do not experience an increase in adverse events; or

(ii) experience an adverse event profile similar in nature and severity to patients receiving the PEGylated uricase over a 120-minute infusion period and an infusion volume of 250 mL.

7. The ~~method~~use of claims 1 or 2, ~~further comprising administering~~ wherein folic acid is to be further administered to said patient at a dosage of 1 mg per day.

8. The ~~method~~use of claims 1 or 2, ~~further comprising~~wherein an altered dosage of MTX is to be administered, wherein the altered dosage comprises:

~~administering~~ folic acid is to be administered to said patient at a dosage of about 1 mg per day; or

~~administering~~ MTX is to be administered to said patient at a dosage of about 7.5 mg twice per day; or

~~administering~~ MTX is to be administered to said patient at a dosage of about 10 mg, wherein the altered dosage of MTX is based on laboratory findings.

9. The ~~method~~use of claim 8, wherein the altered dosage of MTX comprises a temporary stop for laboratory parameters selected from the group consisting of WBC levels of less than about 3.0 x 10^9/L, platelet levels of less than about 50 x 10^9/L, hematocrit levels of less than about 27%, AST/ALT levels of greater than about 2x upper limit of normal (ULN), and eGFR levels of less than 30 mL/min/1.73 m^2, wherein the altered dosage of MTX comprises a reduction in the dosage of MTX to 10 mg per week for laboratory parameters selected from the group consisting of: WBC levels of from about 3.0 x 10^9/L to about 3.5 x 10^9/L and AST/ALT levels of between about 1.5 and about 2x ULN.

10. The ~~method~~use of claims 1 or 2, ~~further comprising~~wherein a prophylactic regimen of colchicine is to be administered for a period of at least 2 weeks prior to the first administration of the PEGylated uricase.

11. The ~~method~~use of any of claims 1 to 10, wherein the SUA levels of the patient are to be determined prior to each dose of the PEGylated uricase.

12. The ~~method~~use of any of claims 1 to 10, ~~further comprising measuring~~wherein one or more of trough PEGylated uricase levels, anti-PEGylated uricase antibody levels, and anti-PEG antibody levels is to be measured, prior to each dose of the PEGylated uricase after the first dose.

13. The ~~method~~use of claims 1 or 2, ~~further comprising measuring~~wherein hematology and liver function are to be measured during treatment.

14. The ~~method~~use of any of claims 1 to 13, wherein said co-administration of the PEGylated uricase and MTX results in normalization of the SUA level in the patient relative to a patient not receiving co-administration of the PEGylated uricase and MTX immunosuppressive therapy.

15. The ~~method~~use of any of claims 1 to 14, wherein the SUA level is reduced to less than 6 mg/dL as a result of co-administration of the PEGylated uricase and MTX immunosuppressive therapy.

16. The ~~method~~use of any of claims 1 to 15, wherein the SUA level is reduced to less than 5 mg/dL as a result of co-administration of the PEGylated uricase and MTX immunosuppressive therapy.

17. The ~~method~~use of any of claims 1 to 16, wherein the SUA level is reduced to less than 2 mg/dL as a result of co-administration of the PEGylated uricase and MTX immunosuppressive therapy.

18. The ~~method~~use of any of claims 1 to 17, wherein the incidence of infusion reaction, gout flare, or anaphylaxis is reduced as a result of co-administration of the PEGylated uricase and MTX immunosuppressive therapy.

19. The ~~method~~use of any of claims 1 to 18, wherein the level of MTX metabolite is increased relative to a patient not receiving co-administration of the PEGylated uricase and MTX immunosuppressive therapy.

20. The ~~method~~use of any of claims 1 to 19, wherein the mean titer of anti-PEGylated uricase antibodies is less than or equal to 1:6000 as a result of co-administration of the PEGylated uricase and MTX immunosuppressive therapy.

21. The ~~method~~use of any of claims 1 to 20, wherein the serum uric acid level is normalized by week 12 after co-administration of PEGylated uricase and MTX treatment begins.

22. The ~~method~~use of any one of the preceding claims, wherein the MTX is to be administered orally.

23. The ~~method~~use of any one of the preceding claims, wherein MTX is to be administered for a period of 2 weeks prior to a first administration of a PEGylated uricase.

24. The ~~method~~use of claim 1, wherein MTX is to be administered for a period of 3 weeks prior to a first administration of a PEGylated uricase.

25. The ~~method~~use of claim 1, wherein MTX is to be administered for a period of 4 weeks prior to a first administration of a PEGylated uricase.

26. The ~~method~~use of any one of the preceding claims, wherein the PEGylated uricase is to be administered over an infusion period of 30, 45, or 60 minutes.

27. The ~~method~~use of claim 1, wherein the PEGylated uricase is to be administered at a dose of about 8 mg.

28. The ~~method~~use of claim 1, wherein the PEGylated uricase is to be administered at a dose of about 12 mg.

29. The ~~method~~use of claim 1, wherein the PEGylated uricase is to be administered at a dose of about 16 mg.

30. The ~~method~~use of claim 1, wherein the PEGylated uricase is to be administered at a dose of about 20 mg.

31. The ~~method~~use of claim 1, wherein the PEGylated uricase is to be administered at a dose of about 24 mg.

32. The ~~method~~use of claim 1, wherein the PEGylated uricase is to be administered at a dose of about 28 mg.

33. The ~~method~~use of claim 1, wherein the PEGylated uricase is to be administered at a dose of about 32 mg.

34. ~~A method of~~Use of methotrexate (MTX) and a PEGylated uricase is the manufacture of a medicament for treating gout in a patient having a serum uric acid (SUA) level of ≥ 6 mg/dL ~~comprising~~, wherein:

~~administering methotrexate (~~MTX~~)~~ is to be administered to said patient at a single dose of about 15 mg per week for a period of 2 to 4 weeks prior to a first administration of ~~a PEGylated uricase; and~~

~~co-administering~~ the PEGylated uricase; and ~~MTX~~

the PEGylated uricase and MTX are to be co-administered to said patient using a dosage regimen comprising a dose of about 8 mg to about 32 mg of the PEGylated uricase intravenously every 2 to 4 weeks ~~for a total of 6 to 26 doses~~, and a single dose of about 15 mg of MTX per week~~, wherein the co-administered MTX is administered concurrently with each administration of the PEGylated uricase~~;

wherein the PEGylated uricase is to be administered over an infusion period of 60 minutes or less.

35. The use of claim 1, 2, or 34 wherein the gout is chronic refractory gout.