adequate body stores of iron. Side effects typically include gastrointestinal problems, such as diarrhea, nausea, bloating and abdominal discomfort. Additionally, because of the frequency in which they are typically given, oral ferrous forms pose a tablet burden on patients and have significant negative gastrointestinal side effects, which lead to non-compliance with oral treatment regimens (Mehdi *et al.*, *supra*).

An alternative is to administer intravenous iron to CKD patients. Some studies have shown that intravenous iron formulations are more effective than either oral ferric iron supplements or oral ferrous iron supplements for treating iron deficiency and/or anemia in CKD patients (Mehdi *et al.*, *supra*). Effective intravenous formulations for the treatment of CKD patients include ferric carboxymaltose, ferumoxytol, ferric gluconate, iron sucrose, and iron dextran. However, intravenous iron is associated with short-term risks such as anaphylaxis and death, as well as with long-term toxicity, including the development of atherosclerosis, infection, and increased mortality (Quinibi *Arzneimittelforschung* (2010) 60:399-412). Further, many CKD clinics, particularly community sites, are ill-equipped to administer intravenous iron because they lack the infrastructure of a dialysis center. This has left a majority of CKD iron-deficient patients without intravenous iron treatment.

Thus, there is need to develop improved methods for treatment of CKD patients.

SUMMARY

Certain aspects of the disclosure provide clinically safe and effective phosphate binders that can be used to reduce and/or control serum phosphorus levels, increase serum bicarbonate levels, improve one or more iron storage parameters (e.g., increase serum ferritin levels, increase transferrin saturation (TSAT), increase hemoglobin concentration) increase iron absorption, maintain iron stores, treat iron deficiency, treat anemia, reduce the need for IV iron and/or reduce the need for erythropoiesis-stimulating agents (ESAs) in CKD patients, including non-dialysis CKD (ND-CKD) patients and end state renal disease (ESRD) patients. In certain examples, the phosphate binder is clinically safe and effective for long term administration to CKD patients, for example up to and including at least 56 weeks of continuous administration.

In a first aspect the present invention is directed to the use of ferric citrate in the manufacture of a medicament for treating anemia in a non-dialysis chronic kidney disease human patient by oral administration of one or more ferric citrate tablets to the patient per day, wherein each tablet comprises approximately 1 g of ferric citrate, and wherein the ferric citrate is a complex comprising iron (III) and citrate with a molar ratio of 1:0.69 to 1:0.87. In accordance with certain examples of the disclosure, a candidate for administrative marketing approval as a phosphate binder is the ferric citrate disclosed herein (also known as KRX-0502 (ferric citrate), see Example 1). Pre-clinical studies have demonstrated the ability of the ferric citrate disclosed herein to bind dietary phosphorus, to decrease intestinal absorption of dietary phosphorus and to reduce serum phosphate levels~~use of ferric citrate in the manufacture of a medicament for reducing serum phosphorus by oral administration to a chronic kidney disease (CKD) patient at a dose of ferric iron ranging from 210 mg–2,520 mg, wherein the ferric citrate provides a mean reduction in serum phosphorus in said CKD patient of 2.00–2.50 mg/dl.~~

In a second aspect, the present invention is directed to the use of ferric citrate in the manufacture of a medicament for increasing serum bicarbonate by oral administration to a chronic kidney disease (CKD) patient at a dose of ferric iron ranging from 210 mg - 2,520 mg, wherein the ferric citrate provides an increase in serum bicarbonate in said CKD patient of 0.1 - 1.0 mEq/L.

In a third aspect, the present invention is directed to the use of ferric citrate in the manufacture of a medicament for increasing iron absorption by oral administration to a chronic kidney disease (CKD) patient in an amount ranging from 1 g to 18 g, wherein the ferric citrate provides for an increase in iron absorption in said CKD patient.

In a fourth aspect, the present invention is directed to the use of ferric citrate in the manufacture of a medicament for maintaining iron stores by oral administration to a chronic kidney disease (CKD) patient in an amount ranging from 1 g to 18 g, wherein the ferric citrate provides for maintenance of iron stores in said CKD patient.

In a fifth aspect, the present invention is directed to the use of ferric citrate in the manufacture of a medicament for improving at least one iron storage parameter by oral administration to chronic kidney disease (CKD) patient in an amount ranging from 1 g to 18 g, wherein the ferric citrate provides for an improvement in at least one iron storage parameter in said CKD patient.

In a sixth aspect, the present invention is directed to the use of ferric citrate in the manufacture of a medicament for treating iron deficiency by oral administration to a chronic kidney disease (CKD) patient in an amount ranging from 1 g to 18 g, wherein the ferric citrate provides for treatment of iron deficiency in said CKD patient.

In a seventh aspect, the present invention is directed to the use of ferric citrate in the manufacture of a medicament for reducing intravenous (IV) iron use by oral administration to an end-stage renal disease (ESRD) patient at a dose of ferric iron ranging from 210 mg - 2,520 mg, wherein the ferric citrate reduces the need for the ESRD patient to be administered IV iron by an amount ranging from 40 - 60 %.

In a eight aspect, the present invention is directed to the use of ferric citrate in the manufacture of a medicament for reducing use of erythropoiesis-stimulating agents (ESAs) by oral administration to an end-stage renal disease (ESRD) patient at a dose of ferric iron ranging from 210 mg - 2,520 mg, wherein the ferric citrate reduces the need for the ESRD patient to be administered one or more ESAs by an amount ranging from 20 - 30 %.

In a ninth aspect, the present invention is directed to an oral iron supplement, comprising ferric citrate in an amount effective to increase iron absorption, maintain iron stores, improve

one or more iron storage parameters, treat iron deficiency or treat anemia in chronic kidney disease patients.

In accordance with certain examples of the disclosure, a candidate for administrative marketing approval as a phosphate binder is the ferric citrate disclosed herein (also known as KRX-0502 (ferric citrate), see Example 1). Pre-clinical studies have demonstrated the ability of the ferric citrate disclosed herein to bind dietary phosphorus, to decrease intestinal absorption of dietary phosphorus and to reduce serum phosphate levels

to dialysis and, in some embodiments, patients who have been subjected to dialysis but who are not undergoing dialysis during the administration of ferric citrate.

In various aspects, ESRD patients are typically those who have been diagnosed with a late stage of chronic kidney disease. In some instances the phrase "end-stage renal disease" is used to indicate the fifth stage of CKD. Therefore, as used herein, an ESRD patient is a patient who has an advanced stage of CKD, such as stage 5, and who has begun either hemodialysis or peritoneal dialysis and/or who has been recommended for kidney transplantation by a health care provider.

In some embodiments, CKD patients display one or more of the following characteristics: a serum phosphorus level between 2.5 mg/dL and 8.0 mg/dL; a serum phosphorus level greater than or equal to 6.0 mg/dL when removed from a phosphate binder; are taking 3 to 18 pills/day of calcium acetate, calcium carbonate, lanthanum carbonate, sevelamer (carbonate or hydrochloride or equivalent sevelamer powder), any other agent serving as a phosphate binder, or a combination of any of the foregoing; have a serum ferritin level that is less than 1000 ~~mg~~micrograms/L; have a transferrin saturation level (TSAT) that is less than 50% at screening; have a life expectancy of more than 1 year; or a combination of any of the foregoing.

In addition, CKD patients may be taking phosphorus binding agents other than ferric citrate, though this is not required. The CKD patients can be mammals and, in some embodiments, are humans. In some embodiments, CKD patients are female or male of any age and/or weight. In some embodiments, CKD patients are males or non-pregnant, non-breastfeeding females who are at least 18 years of age and have been on thrice-weekly hemodialysis and/or peritoneal dialysis for at least 3 months.

Serum Phosphorus

Phosphate is critical for a vast array of cellular processes. It is one of the major components of the skeleton and an integral component of the nucleic acids that make up DNA and RNA. In addition, the phosphate bonds of adenosine triphosphate (ATP) carry the energy required for all cellular functions. Phosphate functions as a buffer in bone, serum, and urine and the addition and/or deletion of phosphate groups to/from enzymes and proteins are common mechanisms for the regulation of their activity. Given the breadth of influence phosphate has, its homeostasis is understandably a highly regulated process.

Patients with CKD typically demonstrate elevated levels of serum phosphate. In non-CKD patients, normal serum phosphate levels should be between 0.81 mmol/L and 1.45

CLAIMS

1. Use of ferric citrate in the manufacture of a medicament for treating anemia in a non-dialysis chronic kidney disease human patient by oral administration of one or more ferric citrate tablets to the patient per day, wherein each tablet comprises approximately 1 g of ferric citrate, and wherein the ferric citrate is a complex comprising iron (III) and citrate with a molar ratio of 1:0.69 to 1:0.87.

2. The use according to claim 1, wherein the anemia is iron deficiency anemia.

3. The use according to claim 1 or 2, wherein hemoglobin concentration is increased or maintained in said non-dialysis chronic kidney disease human patient.

4. The use according to claim 1, 2 or 3, wherein the patient prior to administration of the one or more ferric citrate tablets has a hemoglobin concentration of greater than 9.5 g/dL and less than 11.5 g/dL.

5. The use according to claim 3 or 4, wherein the administration of one or more ferric citrate tablets results in a mean increase in hemoglobin concentration of greater than 0.4 g/dL.

6. The use according to claim 3 or 4, wherein the administration of one or more of ferric citrate tablets results in a mean increase in hemoglobin concentration of 0.4 g/dL to 1 g/dL.

7. The use according to claim 1 or 2, wherein the one or more ferric citrate tablets provides a hemoglobin level in the patient that is at or above a level selected from 11.0 g/dl, 11.5 g/dl, 12.0 g/dl, and 13.0 g/dl.

8. The use according to claim 1 or 2, wherein the one or more ferric citrate tablets provides a hemoglobin level in the patient that is at or above a level selected from 6.8 mmol/L, 7.1 mmol/L, 7.4 mmol/L, and 8.1 mmol/L.

9. The use according to any one of claims 1 to 8, wherein the one or more ferric citrate tablets reduces at least one symptom of iron deficiency selected from fatigue, dizziness, pallor, hair loss, irritability, weakness, pica, brittle or grooved nails, Plummer- Vinson

syndrome, impaired immune function, pagophagia, restless legs syndrome and combinations thereof.

10. The use according to any one of claims 1 to 9, wherein the patient is not receiving intravenous iron and/or erythropoesis-stimulating agents.

11. The use according to any one of claims 1 to 10, wherein the patient prior to administration of the one or more ferric citrate tablets has a serum ferritin concentration of less than 200 ng/mL.

12. The use according to any one of claims 1 to 11, wherein 1 to 12 ferric citrate tablets are administrated to the patient per day.

13. The use according to any one of claims 1 to 12, wherein the one or more ferric citrate tablets is administered within 1 hour of the ingestion of a meal or snack by the patient.

14. The use according to any one of claims 1 to 13, wherein each tablet comprises approximately 80% to approximately 92% by weight of ferric citrate.

15. The use according to any one of claims 1 to 13, wherein each tablet comprises approximately 85% to approximately 92% by weight of ferric citrate.

16. The use according to any one of claims 1 to 13, wherein each tablet comprises approximately 90% to approximately 92% by weight of ferric citrate.

17. The use according to any one of claims 1 to 16, wherein each tablet comprises approximately 4.5% to approximately 30% of binder, wherein the binder is partially or fully pregelatinized starch.

18. The use according to any one of claims 1 to 17, wherein each tablet comprises approximately 0.5% to approximately 3% by weight of a lubricant.

19. The use according to claim 18, wherein the lubricant is calcium stearate.

20. The use according to any one of claims 1 to 19, wherein the water content of each tablet, as measured by loss on drying (LOD), is less than 10% water w/w.

21. The use according to any one of claims 1 to 20, wherein at least 80% of the ferric citrate in each tablet is dissolved in less than or equal to 60 minutes as measured by test method USP <711>.

22. The use according to any one of claims 1 to 13, wherein each tablet comprises:

(a) a core comprising 80% to 90% by weight of ferric citrate, 8% to 15% by weight of pregelatinized starch, and 1% to 3% by weight of calcium stearate; and

(b) a coating.

23. The use according to any one of claims 1 to 22, wherein the patient does not have hyperphosphatemia.

CLAIMS

1. Use of ferric citrate in the manufacture of a medicament for reducing serum phosphorus by oral administration to a chronic kidney disease (CKD) patient at a dose of ferric iron ranging from 210 mg -2,520 mg, wherein the ferric citrate provides a mean reduction in serum phosphorus in said CKD patient of 2.00 - 2.50 mg/dl.

2. The use of claim 1, wherein the ferric citrate provides:

a mean reduction in serum phosphorus in said CKD patient selected from 1.90, 1.91, 1.92, 1.93, 1.94, 1.95, 1.96, 1.97, 1.98, 1.99, 2.00, 2.01, 2.02, 2.03, 2.04, 2.05, 2.06, 2.07, 2.08, 2.09 and 2.10 mg/dl when administered for a period of 12 weeks; or

a mean reduction in serum phosphorus in said CKD patient selected from 2.10, 2.11, 2.12, 2.13, 2.14, 2.15, 2.16, 2.17, 2.18, 2.19, 2.20, 2.21, 2.22, 2.23, 2.24 and 2.25 mg/dl when administered for a period of 24 weeks; or

a mean reduction in serum phosphorus in said CKD patient selected from 2.10, 2.11,

2.12, 2.13, 2.14, 2.15, 2.16, 2.17, 2.18, 2.19 and 2.20 mg/dl when administered for a period of 36 weeks;

a mean reduction in serum phosphorus in said CKD patient selected from 1.95, 1.96, 1.97, 1.98, 1.99, 2.00, 2.01, 2.02, 2.03, 2.04, 2.05, 2.06, 2.07, 2.08, 2.09, 2.10, 2.11, 2.12, 2.13, 2.14 and 2.15 mg/dl when administered for a period of 48 weeks; or

a mean reduction in serum phosphorus in said CKD patient selected from 1.95, 1.96, 1.97, 1.98, 1.99, 2.00, 2.01, 2.02, 2.03, 2.04, 2.05, 2.06, 2.07, 2.08, 2.09, 2.10, 2.11, 2.12,

2.13, 2.14, 2.15, 2.16, 2.17, 2.18, 2.19, 2.20, 2.21, 2.22, 2.23, 2.24, 2.25, 2.26, 2.27, 2.28, 2.29 and 2.30 mg/dl when administered for a period of 52 weeks.

3. Use of ferric citrate in the manufacture of a medicament for increasing serum bicarbonate by oral administration to a chronic kidney disease (CKD) patient at a dose of ferric iron ranging from 210 mg - 2,520 mg, wherein the ferric citrate provides an increase in serum bicarbonate in said CKD patient of 0.1 - 1.0 mEq/L.

4. The use of claim 3, wherein the ferric citrate provides a mean increase in serum bicarbonate concentration in said CKD patient selected 0.70, 0.71, 0.72, 0.73, 0.74, 0.75, 0.76, 0.77, 0.78, 0.79 and 0.80 mEq/L when administered for a period of at least 52 weeks.

5. Use of ferric citrate in the manufacture of a medicament for increasing iron absorption by oral administration to a chronic kidney disease (CKD) patient in an amount ranging from 1 g to 18 g, wherein the ferric citrate provides for an increase in iron absorption in said CKD patient.

6. Use of ferric citrate in the manufacture of a medicament for maintaining iron stores by oral administration to a chronic kidney disease (CKD) patient in an amount ranging from 1 g to 18 g, wherein the ferric citrate provides for maintenance of iron stores in said CKD patient.

7. Use of ferric citrate in the manufacture of a medicament for improving at least one iron storage parameter by oral administration to chronic kidney disease (CKD) patient in an amount ranging from 1 g to 18 g, wherein the ferric citrate provides for an improvement in at least one iron storage parameter in said CKD patient.

8. The use of claim 7, wherein the at least one iron storage parameter is selected from hematocrit, hemoglobin concentration, total iron-binding capacity, transferrin saturation, serum iron levels, liver iron levels, spleen iron levels, serum ferritin levels and combinations thereof.

9. The use of claim 7 or 8, wherein the at least one iron storage parameter is hematocrit and wherein improving comprises increasing the hematocrit of said CKD patient.

10. The use of claim 7 or 8, wherein the at least one iron storage parameter is hemoglobin concentration and wherein improving comprises increasing the hemoglobin concentration in said CKD patient.

11. The use of claim 10, wherein the ferric citrate is administered at a dose of ferric iron ranging from 210 mg - 2,520 mg, and wherein the ferric citrate provides a mean increase in hemoglobin concentration in said CKD patient of 0.3 - 0.6 g/dl.

12. The use of claim 7 or 8, wherein the at least one iron storage parameter is total iron-binding capacity and wherein improving comprises decreasing the total iron-binding capacity in said CKD patient.

13. The use of claim 7 or 8, wherein the at least one iron storage parameter is transferrin saturation (TSAT) and wherein improving comprises increasing the transferrin saturation in said CKD patient.

14. The use of claim 13, wherein the ferric citrate is to be administered at a dose of ferric iron ranging from 210 mg - 2,520 mg, and wherein the ferric citrate provides a mean increase in TSAT in said CKD patient of 5 - 10 %.

15. The use of claim 7 or 8, wherein the at least one iron storage parameter is serum iron levels and wherein improving comprises increasing the serum iron levels in said CKD patient.

16. The use of claim 7 or 8, wherein the at least one iron storage parameter is liver iron levels and wherein improving comprises increasing the liver iron levels in said CKD patient.

17. The use of claim 7 or 8, wherein the at least one iron storage parameter is spleen iron levels and wherein improving comprises increasing the spleen iron levels in said CKD patient.

18. The use of claim 7 or 8, wherein the at least one iron storage parameter is serum ferritin levels and wherein improving comprises increasing the serum ferritin levels in said CKD patient.

19. The use of claim 18, wherein the ferric citrate is to be administered at a dose of ferric iron ranging from 210 mg - 2,520 mg, wherein the ferric citrate provides a mean increase in serum ferritin in said CKD patient of 100 - 400 ng/ml.

20. Use of ferric citrate in the manufacture of a medicament for treating iron deficiency by oral administration to a chronic kidney disease (CKD) patient in an amount ranging from 1 g to 18 g, wherein the ferric citrate provides for treatment of iron deficiency in said CKD patient.

21. The use of claim 20, wherein the ferric citrate reduces at least one symptom of iron deficiency selected from fatigue, dizziness, pallor, hair loss, irritability, weakness, pica, brittle or grooved nails, Plummer- Vinson syndrome, impaired immune function, pagophagia, restless legs syndrome and combinations thereof.

22. The use of claim 20, wherein the iron deficiency treated is anemia.

23. The use of claim 22, wherein the ferric citrate provides a hemoglobin level in the CKD patient that is at or above a level selected from 11.0 g/dl, 11.5 g/dl, 12.0 g/dl, and 13.0 g/dl.

24. The use of claim 22, wherein the ferric citrate provides a hemoglobin level in the CKD patient that is at or above a level selected from 6.8 mmol/L, 7.1 mmol/L, 7.4 mmol/L, and 8.1 mmol/L.

25. The use of any of the preceding claims, wherein the chronic kidney disease patient is an end stage renal disease (ESRD) patient.

26. The use of any of the preceding claims, wherein the chronic kidney disease patient is a non-dialysis chronic kidney disease (ND-CKD) patient.

27. The use of any of the preceding claims, wherein the ferric citrate has a BET active surface area of from 27.99 m2/g to 32.34 m2/g.

28. The use of any of the preceding claims, wherein the ferric citrate has a BET active surface area selected from 27.99 m2/g, 28.87 m2/g and 32.34 m2/g.

29. The use of any of the preceding claims, wherein the ferric citrate is to be administered in a tablet dosage form.

30. The use of claim 29, wherein the tablet dosage form comprises 1 gram of the ferric citrate.

31. Use of ferric citrate in the manufacture of a medicament for reducing intravenous (IV) iron use by oral administration to an end-stage renal disease (ESRD) patient at a dose of ferric iron ranging from 210 mg - 2,520 mg, wherein the ferric citrate reduces the need for the ESRD patient to be administered IV iron by an amount ranging from 40 - 60 %.

32. The use of claim 31, wherein the ferric citrate provides a mean reduction in average cumulative IV iron intake of said ESRD patient is selected from 50, 51, 52, 53, 54, 55, 56, 57, 58, 59 and 60 % when administered for a period of at least 52 weeks.

33. Use of ferric citrate in the manufacture of a medicament for reducing use of erythropolesis-stimulating agents (ESAs) by oral administration to an end-stage renal disease (ESRD) patient at a dose of ferric iron ranging from 210 mg - 2,520 mg, wherein the ferric citrate reduces the need for the ESRD patient to be administered one or more ESAs by an amount ranging from 20 - 30 %.

34. The use of claim 33, wherein the ferric citrate provides a decrease in median ESA intake of said patient is selected from 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 and 30 % when the ferric citrate is administered for a period of at least 52 weeks.

35. The use of any of claim 31-34, wherein the ferric citrate is to be administered in a 1 gram tablet dosage form, each dosage form comprising 210 mg of ferric iron.

36. The use of claim 35, wherein the ESRD patient is to be administered up to 18 tablet dosage forms per day.

37. The use of claim 35, wherein the ESRD patient is to be administered 6 tablet dosage forms per day.

38. The use of any of claims 31-37, wherein the ferric citrate is to be administered within 1 hour of the ingestion of a meal or snack by the patient.

39. The use of any of claims 31-38, wherein the ESRD patient was treated with thrice-weekly hemodialysis or with peritoneal dialysis for at least 3 months prior to administration of the ferric citrate.

40. An oral iron supplement, comprising ferric citrate in an amount effective to increase iron absorption, maintain iron stores, improve one or more iron storage parameters, treat iron deficiency or treat anemia in chronic kidney disease patients.

41. The oral iron supplement of claim 40, wherein the supplement comprises a tablet.

42. The oral iron supplement of claim 40 or 41, wherein the tablet comprises at least 70 wt ferric citrate.

43. The oral iron supplement of any of claims 40-42, comprising at least about 500 mg ferric citrate.