1. Name of the medicinal product

Ferobin Blood Tonic

2. Qualitative and quantitative composition

Ferric Ammonium Citrate BP……. 200mg (equivalent to 43mg of Elemental Iron)
Folic acid …….. 0.5mg
Vitamin B1 …… 2.0mg
Vitamin B2 ……..……. 1.0mg
Vitamin B6 …….. 2.0mg
Vitamin B12 ……. 5.0mg
Nicotinamide ……..….. 5.0mg
Zinc Gluconate ……...… 1.0mg
Manganese Gluconate ……..…….. 1.5mg

3. Pharmaceutical form

Syrup

4. Clinical particulars

4.1 Therapeutic indications

Ferobin plus syrup is indicated for:

- Iron deficiency anaemia
- Megaloblastic anaemia
- Anaemia due to pregnancy
- Anaemia due to excessive or repeated hemorrhage
- Anaemia associated with infections and malignant diseases.

4.2 Posology and method of administration

Method of administration

Adults: 5ml three times or four times daily. Dosage is adjusted gradually, as needed and as tolerated.

Use this medicine only as directed. Do not use it more often and do not use it for a longer period of time than recommended on the label, unless otherwise directed by your doctor.

Keep this medicine away from the eyes. If you should accidentally get some in your eyes, flush them

Ferobin plus syrup can be administered with or without food

4.3 Contraindications

Hypersensitivity to Ferobin plus syrup and the components listed in section 6.1

4.4 Special warnings and precautions for use

(i) Patients post-gastrectomy have poor absorption of iron.

(ii) Caution is advised when prescribing iron preparations to individuals with history of peptic ulcer.

(iii) Duration of treatment should generally not exceed 3 months after correction of anaemia.

(iv) Co-existing deficiency of vitamin B12 or folic acid should be ruled out since combined deficiencies produce microcytic blood film.

(v) Iron deficiency in a male patient warrants careful investigation to determine its cause which forms the basis of primary treatment.

(vi) Iron preparations colour the faeces black, which may interfere with tests used for detection of occult blood in the stools.

(vii) Prolonged or excessive use in children without medical supervision may lead to toxic accumulation

4.5 Interaction with other medicinal products and other forms of interaction

Drug Interactions

Although certain medicines should not be used together at all, in other cases two different medicines may be used together even if an interaction might occur. In these cases, your doctor may want to change the dose, or other precautions may be necessary. Tell your healthcare professional if you are taking any other prescription or nonprescription (over-the-counter [OTC]) medicine.

Other Interactions

Certain medicines should not be used at or around the time of eating food or eating certain types of food since interactions may occur. Using alcohol or tobacco with certain medicines may also cause interactions to occur. Discuss with your healthcare professional the use of your medicine with food, alcohol, or tobacco.

4.6 Pregnancy and lactation

Pregnancy and Lactation

There are no adequate studies in women for determining infant risk when using this medication during pregnancy and breastfeeding. Weigh the potential benefits against the potential risks before taking this medication while pregnant or breastfeeding. It is to note that an overdose of iron can cause miscarriage, birth defects, or pregnancy-related diabetes.

4.7 Effects on ability to drive and use machines

Not applicable

4.8 Undesirable effects

Side effects to this product are rare, but may include temporary staining of the teeth, rash and mild gastrointestinal disturbance.

Reporting of suspected adverse reactions

• Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Report to www.fidson.com

4.9 Overdose

Accidental iron overdose is a leading cause of death in children younger than 6 years old.

An overdose of iron can cause miscarriage, birth defects, or pregnancy-related diabetes.

5. Pharmacological properties

5.1 Pharmacodynamic properties

The complexing properties of iron suggest that KRX-0502 may interact with other orally co-administered drugs, resulting in a decrease in the absorption of the co-administered compound, possibly through the formation of a precipitate with the iron in the gastrointestinal lumen, and the excretion of the formed complex. Such interactions resulting from the properties of KRX-0502 could affect the pharmacokinetics of other drugs and are thus discussed under pharmacokinetic drug interactions

5.2 Pharmacokinetic properties

Due to its main GI effect (iron-phosporous binding), standard PK studies which evaluate plasma concentration, Cmax, AUC and half-life of ferric citrate were not performed. However, since a part of iron and of citrate is absorbed from the GI following oral administration of Fexeric, TK data (serum iron, ferritin, TSAT, TIBC, UIBC) have been derived from the toxicology studies performed on rat and dog: one 4-week non-GLP study in rats, two GLP 90-day to 32-week duration studies in rats, one 4-week non-GLP study in dogs, and two GLP 16- to 42-week duration studies in dogs. The methods of analysis used and Validation procedures are considered adequate. In rats, no changes in iron parameters occurred after 4 weeks treatment with KRX-0502 at doses up to 3 500 mg/kg. Serum iron and TSAT increased significantly in males after 13 weeks treatment at doses of 1400-2800 mg/kg/day, while this effect was noted in females after 33 weeks only. Serum iron and TSAT tended to return towards basal values for males at 33 weeks. Ferritin levels increased at doses of 2800 mg/kg/day in both sexes after 13 weeks treatment onwards, with increased values at 33 weeks compared to 13 weeks for both sexes. In dogs, iron parameters were not affected after 4 weeks of treatment with doses of KRX-0502 of

500 or 1 000 mg/kg/day (N=1 for control, N=2 for treated groups). In studies of longer duration, increases in serum iron levels and TSAT occurred in both sexes at doses of 2 800 mg/kg/day for 16 weeks and 2 000 mg/kg for ≥ 29 weeks. Ferritin levels were increased time- and dose-dependently at doses of 1000 mg/kg/day for 42 weeks and 2000 mg/kg/day for ≥ 16 weeks in males and 400 mg/kg/day for 42 weeks; 1000 mg/kg/day for ≥ 29 weeks; ≥ 2000 mg/kg/day for ≥ 16 weeks in females. Pharmacokinetic parameters of iron and of citrate absorption following oral administration of ferric citrate are sparsely described in the literature. Iron absorption in rats peaked at less than 0.5% of a 0.5 mg dose 1 hour after administration. Plasma iron levels in dogs peaked at less than 5% of a dose of 2 mg ferric citrate 98 min after treatment in normal animals, increasing to 25% after 66 min in iron-deficient dogs. In comparison, iron retained in humans 2 weeks after oral administration of 100 mg iron as ferric citrate to an empty stomach was 1.58% of the initial dose. Absorption is affected by dietary ingredients, although the magnitude of the effect depends on study design and duration. In a single-meal study, mean group absorption ranged from 6.1% for volunteers taking a standard diet, to 2.3% when absorption inhibitors are present in the diet, to 13.5% when the diet included absorption enhancers. However, in a 2-week study, when homeostatic regulatory mechanisms can influence uptake from the GI tract, mean absorption ranged from 6.1% for volunteers taking standard meals to 3.2% when absorption inhibitors are present in the diet, to 8.0% when the diet included absorption enhancers. Citrate is present in low concentrations in circulation and is excreted rapidly upon exogenous administration. In humans, plasma concentrations are approximately 0.1 mM (18.9 µg/mL). In the dog, reported citrate concentrations, measured in whole blood, range from 9 to 19 µg/mL; while in rabbits citrate concentrations, measured in serum, are reported to be higher (70 to 140 µg/mL). Citrate is quickly absorbed following oral administration to humans, peaking at 30 min. Data suggests that normal circulating citrate concentrations are relatively independent of normal dietary citrate intake; however, plasma and urine citrate levels increase following oral doses in the range of about 8.6 to 55 mEq citric acid or potassium citrate. Literature data show that iron in the blood is bound to transferrin, which protects the body from the oxidative properties of iron. Serum iron (ie, iron bound to transferrin) represents only a very small proportion of total body iron (about 0.1%). About 45% to 70% of iron is found in the erythrocytes within haemoglobin. Another 7.5% to 15% is found in myoglobin in the muscles, in a variety of different enzymes (“haem” and “non-haem”), and in storage form. Iron-requiring cells, primarily cells in the bone marrow involved in erythropoiesis and liver cells have membrane-bound transferrin receptors by which iron is transported into the cell. Most stored iron is in the form of ferritin, found in the liver, bone marrow, spleen, and muscles. Such iron distribution pattern is confirmed by the histopathological assessments performed during the toxicology studies performed with KRX-0502/JTT-751 in rats and dogs. Following chronic treatment with ferric citrate, iron deposition was observed in the gastro-intestinal tract, the liver, spleen, kidney, lymph nodes and to a lesser extent, ovaries, pancreas, heart and lungs. In the mouse, 70% of citrate in the body is localized in the bone; while soft tissues do not contain appreciable stores of citrate.

No metabolism study was performed since metabolism of iron and citrate is well established. Physiologically iron that is absorbed is largely conserved; mammals have no physiologic process for iron excretion. Iron losses are small and can occur through skin exfoliation, sloughing off of intestinal cells, menstruation in females, and minimally through biliary and urinary excretion (as reviewed by Geisser, 2011). Iron loss also occurs with haemodialysis. Oral potassium citrate at doses of 30 to 100 mEq/day (3.24 g/day to 10.8 g/day) is used for the treatment of kidney stones, including those associated with hypocitraturia and unduly acidic urine pH (Hall, 2009,Pak, 1994). Upon exogenous administration, citrate is excreted rapidly through the lungs as CO2 and the kidney (80% to 90% of an i.v. dose within 3 hours).

The DDI programme evaluated the in vitro and in vivo (healthy volunteers - see clinical section) interaction of KRX-0502 and the main classes of drug potentially co-administered with it to patients with CKD.

Based on the in vitro visual observation of precipitate occurrence when KRX-0502 is mixed with the drugs, the studies indicate that DDI is likely to occur with drugs of the following classes: antibiotics, anticonvulsant, antidepressant, anti-osteoporosis, anti-parkinsonian and immunosuppressive drugs. The HPLC results generally confirmed those obtained by visual observation and confirmed the interaction of KRX-0502 with cefdinir, ciprofloxacin, doxycyclin and its absence with levofloxacin and vancomycin for antibiotics, as well as the absence of interaction between KRX-0502 and the tested drugs from the following classes: anticoagulants, antidiabetics, anti-hyperlipidemics, treatments of cardiovascular diseases and vitamin D analogues.

5.3 Preclinical safety data

Fexeric (ferric citrate coordination complex, also referred to as KRX-0502, ferric citrate or JTT-751) is an oral iron-based phosphate binder. KRX-0502 reduces intestinal absorption of phosphate as ferric [Fe3+] iron reacts with

ingested phosphate to form an insoluble ferric phosphate complex in the gastrointestinal (GI) tract, which is excreted in the stool. As Fexeric is an iron-based phosphate binder, a small fraction (0.5% to 1%) of the iron is absorbed and assimilated into iron stores.

6. Pharmaceutical particulars

6.1 List of excipients

- Gelatinized sugar
- Methyl Paraben
- Propyl Paraben
- Potassium sorbate
- Sorbitol Solution
- Xanthan gum
- Glycerin
- Propylene glycol
- Caramel cream
- Banana essence
- Purified water qs

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30°C.

Keep all medicines out of reach of children

6.5 Nature and contents of container

200ml glass bottle placed in an inner carton with insert.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. SUPPLIER AND MANUFACTURER

Fidson healthcare Plc,
Km. 38, Lagos-Abeokuta Expressway
Sango Ota, Ogun state
+234 807 700 8888
www.fidson.com
customercare@fidson.com