25.06.2018

רופא/ה רוקח/ת נכבד/ה,
ברצוננו להודיעך על עדכון בעלון לרופא

FERROVIN, solution for injection

חומר פעיל :

One millilitre of solution contains 20 mg of iron as iron sucrose (iron(III)-hydroxide sucrose complex).

להלן עדכונים בעלון לרופא (טקסט מסומן ירוק משמעותו עדכון, טקסט מסומן צהוב משמעותו החמרה, ~~טקסט~~ משמעותו מחיקה):

~~**FERROVIN**~~

~~**INJECTION**~~

~~**SOLUTION**~~

~~**Ferric hydroxide sucrose complex, 20mg/mL**~~

Summary of product characteristics

~~**(SPC)**~~

1. NAME OF THE MEDICINAL PRODUCT

FERROVIN, solution for injection ~~20MG/ML~~

2. QUALITATIVE AND QUANTITATIVE COMPOSITION ~~OF ACTIVE INGREDIENT~~

One millilitre of solution contains 20 mg of iron as iron sucrose (iron(III)-hydroxide sucrose complex).

Each 5mL ampoule of FERROVIN contains ~~20mg/mL Ferric (III) hydroxide Complex with sucrose, quantity equivalent to~~ 100mg iron as iron sucrose (iron(III)-hydroxide sucrose complex) ~~Ferric (III) per ampoule~~.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

~~Injection solution or concentrated s~~Solution for ~~infusion~~injection. ~~in glass ampoule (5mL).~~

FERROVIN is a dark brown, non-transparent, aqueous solution.

~~One carton box containing 5 ampoules.~~

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

FERROVIN is indicated for the therapy of iron deficiency anaemia in the following cases:

Severe iron deficiency only when oral administration has been found impossible. In cases of gastro-intestinal ~~malobsorption~~ malabsorption which rules our oral therapy, patients on dialysis treated with erythropoietin.

4.2 ~~Dosage~~ Posology and method of administration

Monitor carefully patients for signs and symptoms of hypersensitivity reactions during and following each administration of FERROVIN.
FERROVIN should only be administered when staff trained to evaluate and manage anaphylactic reactions is immediately available, in an environment where full resuscitation facilities can be assured. The patient should be observed for adverse effects for at least 30 minutes following each FERROVIN administration (see section 4.4).

Posology
The cumulative dose of FERROVIN must be calculated for each patient individually and must not be exceeded.

Calculation of Dosage:

~~-~~The total ~~additive~~ cumulative dose of FERROVIN, equivalent to the total iron ~~deficiency~~ deficit (mg), is ~~defined~~ determined by the ~~levels of~~ haemoglobin level (Hb) and ~~the~~ body weight (BW). The dose ~~and dosage scheme~~ of FERROVIN ~~should~~ must be ~~individualized~~ individually calculated for each patient ~~based on~~according to ~~the calculation of~~ the total iron ~~deficiency~~deficit calculated with the following Ganzoni formula, for example:

~~Total iron deficiency [mg] = body weight [kg] X (desirable Hb- measured Hb) [g/L] X 0.24* + reserved iron.~~

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Total iron deficit [mg] = BW [kg] X (target Hb- actual Hb) [g/dl] X 2.4* + storage iron [mg]

- ~~Up to~~Below 35 kg ~~body weight~~BW: ~~desirable~~ Target Hb= ~~130g/L~~13g/dl and ~~reserved~~ storage iron= 15mg/kg ~~of body weight~~BW

  ~~Over~~ 35 kg ~~body weight~~BW and above: ~~desirable~~ Target Hb= ~~150g/L~~15g/dl and ~~reserved~~ storage iron= 500 mg

*Factor ~~0.24~~2.4 = 0.0034 (iron content of Hb=0.34%) x 0.07 (blood volume=7% of BW) x 1000 (~~content of hemoglobin in iron ≈ 0.34% ;blood volume ≈ 7% of body weight; factor 1000= diversion~~conversion of [g] ~~in~~to [mg]) x 10.

Total FERROVIN to be administered (in ml)= Total iron deficit [mg]
20 mg iron/ml

Total amount of FERROVIN (ml) to be administered according to body weight, actual Hb level and target Hb level*:

~~The total necessary quantity of FERROVIN is defined either by the above calculation or with the following dosage table (in order to reach a hemoglobin value of 130g/L for body weight <35kg and 150g/L for body weight > 35kg):~~

Body weight [kg]	**Total ~~number~~ amount of FERROVIN ~~ampoules needed~~(20mg iron per ml) to be administered:**			
	Hb ~~60g/L~~6.0 g/dl	Hb ~~75g/L~~7.5 g/dl	Hb ~~90g/L~~9.0 g/dl	Hb ~~105g/L~~10.5 g/dl
~~5~~	~~1.5~~	~~1.5~~	~~1.5~~	~~1~~
~~10~~	~~3~~	~~3~~	~~2.5~~	~~2~~
~~15~~	~~5~~	~~4.5~~	~~3.5~~	~~3~~
~~20~~	~~6.5~~	~~5.5~~	~~5~~	4
~~25~~	~~8~~	~~7~~	~~6~~	~~5.5~~
30	~~9.5~~47.5ml	~~8.5~~42.5ml	~~7.5~~37.5ml	~~6.5~~32.5ml

35	~~12.5~~62.5ml	~~11.5~~57.5ml	~~10~~50ml	~~9~~45ml
40	~~13.5~~67.5ml	~~12~~60ml	~~11~~55ml	~~9.5~~47.5ml
45	~~15~~75ml	~~13~~65ml	~~11.5~~57.5ml	~~10~~50ml
50	~~16~~80ml	~~14~~70ml	~~12~~60ml	~~10.5~~52.5ml
55	~~17~~85ml	~~15~~75ml	~~13~~65ml	~~11~~55ml
60	~~18~~90ml	~~16~~80ml	~~13.5~~67.5ml	~~11.5~~57.5ml
65	~~19~~95ml	~~16.5~~82.5ml	~~14.5~~72.5ml	~~12~~60ml
70	~~20~~100ml	~~17.5~~87.5ml	~~15~~75ml	~~12.5~~62.5ml
75	~~21~~105ml	~~18.5~~92.5ml	~~16~~80ml	~~13~~65ml
80	~~22.5~~112.5ml	~~19.5~~97.5ml	~~16.5~~82.5ml	~~13.5~~67.5ml
85	~~23.5~~117.5ml	~~20.5~~102.5ml	~~17~~85ml	~~14~~70ml
90	~~24.5~~122.5ml	~~21.5~~107.5ml	~~18~~90ml	~~14.5~~72.5ml

Below 35 kg BW: Target HB=13 g/dl

35 kg BW and above: Target Hb=15 g/dl

To convert Hb (mM) to Hb (g/dl), multiply the former by 1.6.

If the total ~~number of ampoules required~~necessary dose exceeds the maximum allowed single ~~daily~~ dose, then the administration ~~has to be split~~must be divided.

~~*Normal p*~~**Posology:**

~~**Children:** 0.15 ml of Ferrovin per kg of body weight per day (=3mg of iron/kg of body weight/day).~~

Adults:

~~1-2 ampoules~~5-10ml of FERROVIN (100-200 mg iron) ~~twice~~ one to three times a week~~,~~. For administration time and dilution ration see "Method of administration", ~~depending upon the hemoglobin level.~~

Paediatric population:

The use of iron sucrose has not been adequately studied in children and, therefore, FERROVIN is not recommended for use in children.

~~*Maximum daily dose*~~

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~~**Children:** 0.35 ml of Ferrovin per kg of body weight per day (=7mg of iron/kg of body weight/day).~~

~~**Adults**: 0.35 ml of Ferrovin per kg of body weight per day (=7mg of iron/kg of body weight/day) up to maximum of 5 ampoules of Ferrovin (500 mg of iron), admixed with 500 ml of 0.9%NaCl solution and infused at least 3 1/2 hours.~~

Method of Administration:

FERROVIN must only be administered by the intravenous route. This may be by a slow intravenous injection, by an intravenous drip infusion or directly into the venous line of the dialysis machine.

~~*Administration:*~~

Intravenous drip ~~Infusion~~infusion:

~~-~~FERROVIN ~~should preferably administered by drip infusion. The content of each ampoule (5 ml = 100 mg)~~ must only be diluted in ~~100 ml of~~sterile 0.9% m/V sodium chloride (NaCl) ~~-~~solution. Dilution must take place immediately prior to ~~administration (2 ampoules in 200 ml etc). The~~infusion and the solution should be ~~infused at a rate of:100 ml in at least 15 minutes; 200 ml in at least 30 minutes; 300 ml in at least 1 1/2 hours ; 400 ml in at least 2 1/2 hours; 500 ml in at least 3 1/2 hours.~~administered as follows:

FERROVIN dose (mg of iron)	FERROVIN dose (ml of FERROVIN)	Maximum dilution volume of sterile 0.9% m/V NaCl solution	Minimum Infusion Time
50 mg	2.5 ml	50 ml	8 minutes
100 mg	5 ml	100 ml	15 minutes
200 mg	10 ml	200 ml	30 minutes

For stability reasons, dilutions to lower FERROVIN concentrations are not permissible.

Intravenous ~~infusion~~injection:

~~-~~FERROVIN ~~can also~~may be administered by slow intravenous injection at a rate of ~~not more than~~ 1 ml undiluted solution per minute ~~(=5 minutes per ampoule),~~and not

exceeding ~~2 ampoules~~10 ml ~~of~~ FERROVIN (200 mg iron) per injection. ~~After injection, extend the arm of the patent. Avoid paravenous application.~~

Injection into ~~dialyser~~venous line of dialysis machine:

~~-~~FERROVIN ~~can~~ may be administered during a haemodialysis session directly into the venous ~~limb~~ line of the ~~dialyser~~ dialysis machine under the same conditions as for intravenous injection. ~~FERROVIN must only be administered intravenously by drip infusion, by slow injection or directly into the venous limb in the dialyser. It is not suitable for intramuscular use, nor is it suitable to be administered as a total dose infusion (see "Precautions for use") due to the risk of an increased occurrence of side effects. All precautions for the treatment of anaphylactic reactions must be available. Before administration of the first therapeutic dose, a test dose of 1/4 to 1/2 ampoule in adults and half the daily dose in children should be administered to test the tolerance. If no adverse reactions occur within a waiting period of at least 15 minutes after administration the remaining portion of the calculated dose can be given. The test injection should be carried out before each administration.~~

4.3 Contra – Indications

The use of FERROVIN~~'s~~ ~~use~~ is contraindicated in the following ~~cases~~conditions:

- ~~non iron deficiency anemia (e/g/ hemolytic anemia, megaloblastic anemia caused by Vit B12 deficiency, disturbances in erythropoesis, hypoplasia of bone marrow)~~
- ~~iron overloading (e.g.haemochromatosis, haemosiderosis) or iron use disturbances (sidero-archrestic anemia, thalassaemia, lead anemia, Porphyria cutanea tarda);~~
- ~~history of hypersensitivity to iron monosaccharide or disaccharide complexes~~
- ~~*Osler-Rendu-Weber syndrome*~~
- ~~*Acute phase of chronic polyarthritis*~~
- ~~*Acute renal* infections~~
- ~~Uncontrolled hyperparathyroidism~~
- ~~Decompensated hepatic cirrhosis; infectious hepatitis.~~
- ~~First trimester of pregnancy~~
- Hypersensitivity to the active substance, to FERROVIN or any of its excipients listed in section 6.1.
- Known serious hypersensitivity to other parenteral iron products.
- Anaemia not caused by iron deficiency.
- Evidence of iron overload or hereditary disturbances in utilization of iron.

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4.4 Special warnings and ~~special~~ precautions for use

~~Hypotension episodes might occur when the injection is delivered with a fast rate.~~

~~If by accident paravenous loss of the drug is observed, and if the needle is still in place, wash with a small quantity of normal saline 0.9%. Cautiously apply a mucoplysacharide gel or ointment to the injection site (cave massage) in order to hasten the emulsion and to avoid spreading of the iron.~~

~~Special care should be taken in the administration of FERROVIN to patients suffering from allergies, asthma, liver or kidney disorders and rheumatoid arthritis.~~

~~Undersible effects can occur in patients with cardiopulmunory diseases which can increase accompanying cardio-vascular complications.~~

~~Venofore must be administered with caution in patients (adults and children) with a sharply elevated ferritin level due to an acute or chronic infection, since parenteral iron may have an unfavourable effect on the course of a bacterial or viral infection. (SPC – Israel)~~

Parenterally administered iron preparations can cause hypersensitivity reactions including serious and potentially fatal anaphylactic/anaphylactoid reactions. Hypersensitivity reactions have also been reported after previously uneventful doses of parenteral iron complexes including iron sucrose. However, in several studies performed in patients who had a history of a hypersensitivity reaction to iron dextran or ferric gluconate, iron sucrose was shown to be well tolerated. For known serious hypersensitivity to other parenteral iron product see section 4.3.

The risk of hypersensitivity reactions is enhanced for patients with known allergies including drug allergies, including patients with a history of severe asthma, eczema or other atopic allergy.

There is also an increased risk of hypersensitivity reactions to parenteral iron complexes in patients with immune or inflammatory conditions (e.g. systemic lupus erythematosus, rheumatoid arthritis).

FERROVIN should only be administered when staff trained to evaluate and manage anaphylactic reactions is immediately available, in an environment where full resuscitation facilities can be assured. Each patient should be observed for adverse effects for at least 30 minutes following each FERROVIN injection. If hypersensitivity reactions or signs of intolerance occur during administration, the treatment must be stopped immediately. Facilities for cardio respiratory resuscitation and equipment for handling acute anaphylactic/anaphylactoid reactions should be available, including

an injectable 1:1000 adrenaline solution. Additional treatment with antihistamines and/or corticosteroids should be given as appropriate.

In patients with liver dysfunction, parenteral iron should only be administered after careful risk/benefit assessment. Parenteral iron administration should be avoided in patients with hepatic dysfunction where iron overload is a precipitating factor, in particular Porphyria Cutanea Tarda (PCT). Careful monitoring of iron status is recommended to avoid iron overload.

Parenteral iron should be used with caution in the case of acute or chronic infection. It is recommended that the administration of FERROVIN is stopped in patients with bacteraemia. In patients with chronic infection, a risk/benefit evaluation should be performed.

Paravenous leakage must be avoided because leakage of FERROVIN at the injection site can lead to pain, inflammation and brown discoloration of the skin.

4.5 Interaction with other medicinal products and other forms of interaction

As with all parenteral iron preparations, FERROVIN should not be administered concomitantly with oral iron preparations, ~~given that~~since the ~~absorbance~~ absorption of ~~the~~ oral iron is ~~decreased~~reduced. ~~Thus~~Therefore, oral iron therapy should ~~not begin before~~be started at least 5 days ~~have passed since~~after the last injection of FERROVIN ~~injection~~.

~~Concomitant administration of ACE inhibitors (e.g. Enalapril) can increase the systemic effects of parenterally administered iron preparations.~~

4.6 ~~Administration during~~Fertility, pregnancy and lactation

Pregnancy

There is no data from the use of iron sucrose in pregnant women in the first trimester. Data (303 pregnancy outcomes) from the use of iron sucrose in pregnant women in the second and third trimester showed no safety concerns for the mother or newborn. A careful risk/benefit evaluation is required before use during pregnancy and FERROVIN should not be used during pregnancy unless clearly necessary (see section 4.4).

Iron deficiency anaemia occurring in the first trimester of pregnancy can in many cases be treated with oral iron. Treatment with FERROVIN should be confined to

second and third trimester if the benefit is judged to outweigh the potential risk for both the mother and the fetus.
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

~~Toxicological studies of FERROVIN in the reproductive cycle of animals has not been yet completed. Ferric dextran has been proved to be teratogenic and embryocide in non-anemic pregnant animals. Therefore, FERROVIN's use is contraindicated during the first trimester of pregnancy. If the benefit of treatment is judged to overweigh the potential risk to the foetus, treatment should be restricted to the second and third trimester.~~

Breast-feeding
~~Unmodified iron polysaccharide complex can pass into mother's milk in small quantities. As no FERROVIN specific data is available, it should be used with caution during lactation.~~

There is limited information on the excretion of iron in human milk following administration of intravenous iron sucrose. In one clinical study, 10 healthy breast-feeding mothers with iron deficiency received 100 mg iron in the form of iron sucrose. Four days after treatment, the iron content of the breast milk had not increased and there was no difference from the control group (n=5). It cannot be excluded that newborns/infants may be exposed to iron derived from FERROVIN via the mother's milk, therefore the risk/benefit should be assessed.

Preclinical data do not indicate direct or indirect harmful effects to the nursing child. In lactating rats treated with ^{59}Fe-labelled iron sucrose, low secretion of iron into the milk and transfer of iron into the offspring was observed. Non metabolised iron sucrose is unlikely to pass into the mother's milk.

Fertility
No effects of iron sucrose treatment were observed on fertility and mating performance in rates.

4.7 Effects on ability to drive and use machines

~~FERROVIN is not expected to affect the ability to drive or use machinery.~~

In the case of symptoms of dizziness, confusion or light headedness following the administration of FERROVIN, patients should not drive or use machinery until the symptoms have ceased.

4.8 ~~Adverse~~ Undesirable ~~effects~~ Effects

~~Occasionally the following undesirable effects can occur: hypotension, fever , phlebitis and vein spasms in the area of the punctured vein, nausea, vomiting, abdominal pain, headache, dizziness, joint pains, swelling of the lymph glands, all of which should be treated symptomatically.~~

~~Allergic or anaphylactic reactions rarely occur, and particularly in patients whith bronchial asthma, with low iron binding capacity and/or folic acid deficiency. In the case of a mild allergic reaction, antihistamines should be administered, in the case of a serious anaphylactic reaction, the patient must receive intensive medical care. It is to be noted that patient simultaneously receiving beta-blockers do not react adequately to adrenaline.~~

The most commonly reported adverse drug reaction in clinical trials with iron sucrose was dysgeusia, which occurred with a rate of 4.5 events per 100 subjects. The most important serious adverse drug reactions associated with iron sucrose are hypersensitivity reactions, which occurred with a rate of 0.25 events per 100 subjects in clinical trials.

The adverse drug reactions reported after the administration of iron sucrose in 4,064 subjects in clinical trials as well as those reported from the post-marketing setting are presented in the table below.

System Organ Class	**Common (≥1/100, <1/10)**	**Uncommon (≥1/1,000, <1/100)**	**Rare (≥1/10,000, <1/1,000)**	**Frequency not known[1)]**
Immune system disorders		Hypersensitivity		Anaphylactoid reactions, angioedema
Nervous system disorders	Dysgeusia	Headache, dizziness, paraesthesia, hypoaesthesia	Syncope, somnolence,	Depressed level of consciousness, confusional state, loss of consciousness, anxiety, tremor
Cardiac disorders			Palpitations	Bradycardia, tachycardia
Vascular disorders	Hypotension, hypertension	Flushing, Phlebitis		Circulatory collapse, thrombophlebitis
Respiratory, thoracic and mediastinal disorders		dyspneoa		Bronchospasm
Renal and			Chromaturia	

urinary disorders				
Gastrointestinal disorders	Nausea	Vomiting, abdominal pain, diarrhoea, constipation		
Skin and subcutaneous tissue disorders		Pruritus, rash		Urticaria, erythema
Musculoskeletal and connective tissue disorders		Muscle cramps, myalgia, arthralgia, pain in extremity, back pain		
General disorders and administration site conditions	Injection /infusion site reaction (2)	Chills, asthenia, fatigue, oedema peripheral, pain	chest pain, hyperdrosis pyrexia,	cold sweat, malaise, pallor
Investigations		Alanine aminotransferase increased, aspartate aminotransferase increased, Gammaglutamyltransferase increased, Serum ferritin increased	blood lactate dehydrogenase increased	

1) Spontaneous reports from the post-marketing setting
2) The most frequently reported are: injection/infusion site pain, -extravasation, -irritation, -reaction,-discolouration, - haematoma, -pruritus.

Reporting of suspected adverse reactions:
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

4.9 Overdos~~ag~~e

Overdos~~ag~~e can cause ~~acute~~ iron overload~~ing with iron that might~~which may ~~be manifested~~manifest itself as haemosiderosis. Overdos~~ag~~e should be ~~dealt~~treated~~-~~, as

deemed necessary by the treating physician, with an iron ~~supportive measures and, if necessary, with an iron-binding,~~ chelating agent or according to standard medical practice.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-anaemic preparation, iron, parenteral preparation,
ATC code: B03AC

~~Iron-kinetics of labeled with ^{59}Fe and ^{52}Fe FERROVIN was estimated at 5 patients with anemia and chronic renal dysfunction. The removal of ^{52}Fe from plasma was ranging from 60 to 100 min. ^{52}Fe was distributed at the liver, spleen and bone marrow. 2 weeks after administration, maximum utility of ^{59}Fe by erythrocytes was ranging from 62-97%.~~

Mechanism of action
Iron sucrose, the active ingredient of FERROVIN, is composed of a polynuclear iron(III)-hydroxide core surrounded by a large number of non-covalently bound sucrose molecules.
The complex has a weight average molecular weight (Mw) of approximately 43 kDa. The polynuclear iron core has a structure similar to that of the core of the physiological iron storage protein ferritin. The complex is designed to provide, in a controlled manner, utilizable iron for the iron transport and storage proteins in the body (i.e., transferrin and ferritin, respectively).
Following intravenous administration, the polynuclear iron core from the complex is taken up predominantly by the reticuloendothelial system in the liver, spleen, and bone marrow. In a second step, the iron is used for the synthesis of Hb, myoglobin and other iron-containing enzymes, or stored primarily in the liver in the form of ferritin.

Clinical efficacy and safety
Chronic kidney disease
Study LU98001 was a single arm study to investigate the efficacy and safety of 100 mg iron as iron sucrose for up to 10 sessions over 3-4 weeks in haemodialysis patients with iron deficiency anaemia (Hb >8 and <11.0 g/dl, TSAT <20%, and serum ferritin ≤300 µg/l) who were receiving rHuEPO therapy. A Hb ≥11 g/dl was attained in 60/77 patients. The mean increase in serum ferritin and TSAT was significant from baseline to the end of treatment (Day 24) as well as to the 2 and 5 weeks follow-up visit.
Study 1VEN03027 was a randomised study comparing iron sucrose (1000 mg in divided doses over 14 days) and oral ferrous sulphate (325 mg 3 times daily for 56 days) in non-dialysis dependent chronic kidney disease patients (Hb≤11.0 g/dl,

serum ferritin ≤300 µg/l, and TSAT ≤25%) with or without rHuEPO. A clinical response (defined as Hb increase ≥1.0 g/dl and serum ferritin increase ≥160 µg/l) was more frequently observed in patients treated with iron sucrose (31/79; 39.2%) compared to oral iron (1/82; 1.2%); p<0.0001.

Inflammatory Bowel Disease
A randomised, controlled study compared iron sucrose (single IV dose of 200 mg iron once per week or every second week until the cumulative dose was reached) with oral iron (200 mg twice daily for 20 weeks) in patients with inflammatory bowel disease and anaemia (Hb <11.5 g/dl). At the end of treatment, 66% of patients in the iron sucrose group had an increase in Hb ≥2.0 g/dl compared to 47% in the oral iron group (p=0.07).

Postpartum
A randomised, controlled trial in women with postpartum iron deficiency anaemia (Hb <9 g/dl and serum ferritin <15 µg/l at 24–48 hours post-delivery) compared 2 × 200 mg iron given as iron sucrose on Days 2 and 4 (n=22) and 200 mg of oral iron given as ferrous sulphate twice daily for 6 weeks (n=21). The mean increase in Hb from baseline to Day 5 was 2.5 g/dl in the iron sucrose group and 0.7 g/dl in the oral iron group (p<0.01).

Pregnancy
In a randomised, controlled study, women in their third trimester of pregnancy with iron deficiency anaemia (Hb 8 to 10.5 g/dl and serum ferritin <13 µg/l) were randomised to iron sucrose (individually calculated total dose of iron administered over 5 days) or oral iron polymaltose complex (100 mg 3× daily until delivery). The increase in Hb from baseline was significantly greater in the iron sucrose group compared to the oral iron group at Day 28 and at delivery (p<0.01).

5.2 Pharmacokinetic properties

~~After intravenous injection to healthy volunteers of 100mg Fe (III) (= 1 ampoule of FERROVIN), maximum levels of Ferric (mean value 538µmol/ L) were achieved 10min after injection. The distribution volume of the central section showed a good relevance to the plasma volume (approximately 3 liters).~~

~~Injected iron was rapidly cleared from plasma, with a final half-life of approximately 6 hours. The distribution volume during the stabilized condition was about 8 liters, showing the poor iron distribution to the body fluids, because of the lower stability of ferric sucrose compared with transferin, resulting to the fact that iron transfer is equal to approximately 31mg Fe(III) / 24 h.~~

~~Clearance of iron from the kidneys, occurring at the first 4h after injection, is equivalent to less than 5% of the total body clearance (approximately 20 ml/min). 4 hours after administration the transferring is saturated to >90% and after 24 hours, the ferritin level has doubled. After 24h the iron levels in plasma were reduced to the ones before injection, while about 75% of the sucrose dose was removed.~~

Distribution

The ferrokinetics of iron sucrose labelled with ^{52}Fe and ^{59}Fe were assessed in 6 patients with anaemia and chronic renal failure. In the first 6–8 hours, ^{52}Fe was taken up by the liver, spleen and bone marrow. The radioactive uptake by the macrophage-rich spleen is considered to be representative of the reticuloendothelial iron uptake. Following intravenous injection of a single 100 mg iron dose of iron sucrose in healthy volunteers, maximum total serum iron concentrations were attained 10 minutes after injection and had an average concentration of 538 µmol/l.
The ~~distribution~~ volume of distribution of the central compartment corresponded well to the volume of plasma (approximately 3 litres).

Biotransformation

Upon injection, sucrose largely dissociates and the polynuclear iron core is mainly taken up by the reticuloendothelial system of the liver, spleen, and bone marrow. At 4 weeks after administration, red cell iron utilization ranged from 59 to 97%.

Elimination

The iron sucrose complex has a weight average molecular weight (Mw) of approximately 43 kDa, which is sufficiently large to prevent renal elimination. Renal elimination of iron, occurring in the first 4 hours after injection of an iron sucrose dose of 100 mg iron, corresponded to less than 5% of the dose. After 24 hours, the total serum iron concentration was reduced to the pre-dose level. Renal elimination of sucrose was about 75% of the administered dose.

5.3 Preclinical safety data ~~on safety (Toxicology)~~

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity and toxicity to reproduction and development.

~~There are no other clinical data concerning the physician apart from those referred to the above paragraphs of the SPC.~~

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide (for pH adjustment)

Water for injection

6.2 ~~Incompatibilities~~Incompatibility

~~FERROVIN should be mixed ONLY with normal saline 0.9%. Neither other dilution solutions or solutions for infusion of the drug are permitted, nor other therapeutic agents, given that there is possibility of sediment formation or/ and interaction. Compatibility with containers not made of glass, PE or PVC is not known.~~This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6. There is the potential for precipitation and/or interaction if mixed with other solutions or medicinal products. The compatibility with containers other than glass, polyethylene and PVC is not known.

6.3 Shelf – life

Shelf-life of the ~~commercially available~~ product as packed for sale:

~~2 years.~~The expiry date of the product is indicated on the packaging materials.

Shelf-life after first opening of the container:

~~By~~ From a microbiological ~~aspect~~point of view, the product should be used ~~instantly~~immediately.

Shelf-life after dilution with sterile 0.9% m/V sodium chloride (NaCl) solution ~~0.9%~~:

Chemical and physical stability for 12h after dilution has been proved at room temperature. ~~By~~ From a microbiological ~~aspect~~point of view, the product should be used ~~instantly~~immediately after dilution with sterile 0.9% m/V sodium chloride solution. If not, the storage times after dilution and the conditions before use are responsibility of the user and should normally not exceed 3h at room temperature, except when the dilution has been performed at controlled and valid aseptic conditions.

6.4 Special precautions for storage

Prescribed storage conditions: ~~Keep~~ Store in the ~~initial paper~~original package. Do not store at temperatures above 25^{0}C. Do not freeze.

For storage conditions after dilution or first opening of the medicinal product, see section 6.3.

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6.5 Nature and content of container

5 ml solution in one ampoule (~~Glass ampoule~~ type I glass) ~~of 5mL~~ in pack sizes of 5.

6.6 ~~Instructions for use and handling~~ Special precautions for disposal and other handling

~~Before use ampoules should be visually checked for any sediment or deterioration. Only ampoules containing an homogenous solution without sediment must be used. Also see **6.3. Shelf-life.**~~

Ampoules should be visually inspected for sediment and damage before use. Use only those containing a sediment free and homogenous solution.

FERROVIN must not be mixed with other medicinal products except sterile 0.9% m/V sodium chloride solution for dilution. For instructions on dilution of the product before administration, see section 4.2.

The diluted solution must appear as brown and clear.

Each ampoule of FERROVIN is intended for single use only.

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

7. MANUFACTURER:

Rafarm S. A.,~~,~~ Greece

12 Korinthou St., 154 51 N Psihiko Athenes, Greece

…[8]

9. LICENSE NUMBER:

141-09-31806-00

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