DESCRIPTION

Overcom™ (Iron sucrose injection, USP) is a brown, sterile, colloidal solution of complex of polynuclear iron (III)-hydroxide in sucrose for intravenous use. Iron sucrose injection has a molecular weight of approximately 34,000 - 60,000 daltons and a proposed structural formula: \([\text{Na}_2\text{Fe}_5\text{O}_8(\text{OH}) \cdot 3(\text{H}_2\text{O})]_n \cdot m(\text{C}_{12}\text{H}_{22}\text{O}_{11})\) where: \(n\) is the degree of iron polymerization and \(m\) is the number of sucrose molecules associated with the iron (III)-hydroxide. The drug product contains approximately 30% sucrose w/v (300 mg/ml) and has a pH of 10.5 - 11.1. The product contains no preservatives. The osmolarity of the injection is between 1150 mOsmol/L to 1350 mOsmol/L.\(^1\)

COMPOSITION

Each 5ml contains:

- Iron Sucrose
- Equivalent to Elemental Iron................................................. 100 mg
- Water for Injection IP..................................................... q.s. to 5 ml

CLINICAL PHARMACOLOGY

Mechanism of action

Overcom™ is used to replenish body iron stores in patients with iron deficiency on chronic hemodialysis who are receiving erythropoietin. Iron is essential to the formation of hemoglobin and to the function and formation of other heme and nonheme compounds. Untreated depletion of iron stores leads to iron-deficient erythropoiesis and in turn to iron deficiency anemia. Administration of Overcom™ replenishes tissue iron stores, reverses iron depletion and iron-deficient erythropoiesis, and corrects or prevents iron deficiency anemia. Following intravenous administration, Overcom™ is dissociated into iron and sucrose by the reticuloendothelial system, and iron is transferred from the blood to a pool of iron in the liver and bone marrow. Ferritin, an iron storage protein, binds and sequesters iron in a nontoxic form, from which iron is easily available. Iron binds to plasma transferrin, which carries iron within the plasma and the extracellular fluid to supply the tissues. The transferrin receptor, located in the cell, and the transferrin-receptor complex is returned to the cell membrane. Transferrin without iron (apotransferrin) is then released to the plasma. The intracellular iron becomes (mostly) hemoglobin in circulating red blood cells (RBCs). Transferrin synthesis is increased and ferritin production reduced in iron deficiency. The converse is true when iron is plentiful.

The stability of Overcom™ allows a competitive exchange of iron between iron sucrose and selective iron-binding proteins such as transferrin and ferritin. Pharmacokinetic parameters show that the administered iron disappears very rapidly from the serum, insuring a rapid correction of iron deficiency anemia.\(^1\)

Pharmacokinetics
In healthy adults treated with intravenous doses of Overcom™, its iron component exhibits first order kinetics with an elimination half-life of 6 h, total clearance of 1.2 L/h, non-steady state apparent volume of distribution of 10.0 L and steady state apparent volume of distribution of 7.9 L. Since iron disappearance from serum depends on the need for iron in the iron stores and iron utilizing tissues of the body, serum clearance of iron is expected to be more rapid in iron deficient patients treated with iron sucrose as compared to healthy individuals. The effects of age and gender on the pharmacokinetics of iron sucrose have not been studied. Overcom™ is not dialyzable through CA210 (Baxter) High Efficiency or Fresenius F80A High Flux dialysis membranes. In in vitro studies, the amount of iron sucrose in the dialysate fluid was below the levels of detection of the assay (less than 2 parts per million).¹

**Distribution:** In healthy adults receiving intravenous doses of iron sucrose, its iron component appears to distribute mainly in blood and to some extent in extravascular fluid. A study evaluating iron sucrose containing 100 mg of iron labeled with ⁵²Fe/⁵⁹Fe in patients with iron deficiency shows that a significant amount of the administered iron distributes in the liver, spleen and bone marrow and that the bone marrow is an iron trapping compartment and not a reversible volume of distribution.

**Metabolism and Elimination:** Following intravenous administration of Overcom™, iron sucrose is dissociated into iron and sucrose by the reticuloendothelial system. The sucrose component is eliminated mainly by urinary excretion. In a study evaluating a single intravenous dose of iron sucrose containing 1,510 mg of sucrose and 100 mg of iron in 12 healthy adults (9 female, 3 male: age range 32-52), 68.3% of the sucrose was eliminated in urine in 4 h and 75.4% in 24 h. Some iron is also eliminated in the urine. Neither transferrin nor transferrin receptor levels changed immediately after the dose administration. In this study and another study evaluating a single intravenous dose of iron sucrose containing 500-700 mg of iron in 26 anemic patients on erythropoietin therapy (23 female, 3 male; age range 16-60), approximately 5% of the iron was eliminated in urine in 24 h at each dose level².

**CLINICAL STUDIES**

**Efficacy and safety of iron sucrose for iron deficiency in patients with dialysis-associated anemia: North American clinical trial³**

In a multicenter North American clinical trial, the efficacy and safety of iron sucrose therapy was determined in 101 patients with dialysis-associated anemia, evidence of iron deficiency, and below-target hemoglobin (Hgb) levels despite epoietin therapy. Evidence of iron deficiency included a transferrin saturation (Tsat) less than 20% and ferritin level less than 300 ng/mL, and below-target Hgb levels included values less than 11.0 g/dl. Iron sucrose was administered in 10 doses, each administered undiluted as 100 mg IV push over 5 minutes, without a prior test dose. Efficacy was assessed by determining the subsequent change in Hgb, Tsat, and ferritin values. Safety was assessed by recording blood pressure and adverse events after iron sucrose injection and comparing results with those for the same patients during an observation control period. Results showed a significant increase in Hgb level that was first evident after three doses of iron sucrose and persisted at least 5 weeks after the 10th dose. Tsat and ferritin levels also increased significantly and remained elevated.

Out of 77 enrolled patients, including those with previous iron dextran sensitivity, other drug allergies, or concurrent angiotensin-converting enzyme inhibitor use, no serious adverse drug reactions and no change in intradialytic blood pressure associated with iron sucrose administration were seen. It was concluded that iron sucrose injection administered as 1,000 mg in 10 divided doses by IV push without a prior test dose was safe and effective for the treatment of iron deficiency in patients with dialysis-associated anemia.

**Safety and efficacy of iron sucrose in patients sensitive to iron dextran: North American clinical trial⁴**

As part of the North American clinical trials for iron sucrose injection, the effect of intravenous (IV) iron sucrose was examined in 23 hemodialysis patients with documented sensitivity to iron dextran, ongoing erythropoietin therapy, and below-target-range
hemoglobin (Hb) levels (<11.0 g/dl). Patients were assigned to treatment groups according to whether reactions had occurred to iron dextran and were judged to be mild (n = 16; group A) or severe (n = 7; group B). Adverse events and vital signs were prospectively examined after administering 100 mg of IV iron sucrose in each of 10 consecutive dialysis treatment sessions and results were compared with those recorded in each of three consecutive dialysis sessions without iron treatment. Iron sucrose was administered by IV push over 5 minutes to group A patients and by IV push over 5 minutes or IV infusion over 15 to 30 minutes to group B patients without a test dose. Results showed no serious adverse drug reactions after a total of 223 doses of iron sucrose (184 doses by IV push, 39 doses by IV infusion). Intradialytic blood pressure changes after IV iron sucrose injection did not differ from those recorded during dialysis sessions without treatment. An increase in values for Hb, hematocrit, transferrin saturation, and ferritin, coupled with no significant change in erythropoietin dose and a decrease in total iron-binding capacity, confirmed the efficacy of iron sucrose injection in managing anemia. It was concluded that iron sucrose injection was safe and effective in the management of anemia in patients sensitive to iron dextran and could be administered without a test dose by IV push or infusion.

Rapid, high-dose intravenous iron sucrose therapy in 2 Jehovah's Witness patients with severe anemia, iron deficiency and chronic kidney disease

In this study, two patients with chronic kidney disease presented with severe anemia and iron deficiency. The regimen included epoietin, folic acid and high-dose intravenous iron sucrose infusions over multiple successive days (total dosages of 2 and 3.5 g). Results showed that the patients' iron stores were replenished and an erythropoietic response ensued subsequent to this aggressive and unique therapeutic regimen. There were no side effects observed which could be attributed to iron sucrose, and both patients stabilized and were discharged after 3 - 4 weeks. It was concluded that in patients with chronic kidney disease who were severely anemic and iron-deficient and where transfusion was not possible, an aggressive regimen of multiple high-dose iron sucrose infusions might be both safe and effective.

Iron sucrose in hemodialysis patients: Safety of replacement and maintenance regimens

This multicenter phase IV clinical trial examined the safety of iron sucrose for the treatment of iron deficiency and for the maintenance of iron sufficiency in hemodialysis patients. In this safety study, iron sucrose was given in two dosing regimens. Iron deficient patients were treated with intravenous iron sucrose, 100 mg, during 10 consecutive hemodialysis sessions (replacement regimen). Iron replete patients were given iron sucrose, 100 mg intravenous (iv) over 5 minutes, weekly for 10 weeks (maintenance regimen). At the end of each 10-dose cycle, iron status was reassessed, and dosing during the subsequent cycle was based on the adequacy of iron stores as per Dialysis Outcome Quality Initiative (K/DOQI) Guidelines. With each dosing regimen, adverse events, if any, were recorded and described. Results showed that six hundred and sixty-five hemodialysis patients, including 80 who had experienced previous intolerance to other parenteral iron preparations, received a total of 8583 doses of iron sucrose. One hundred eighty-eight patients received more than one i.v iron cycle (replacement, maintenance, or both). There were no serious or life-threatening drug-related adverse events. It was concluded that iron sucrose was safe when given as treatment for iron deficiency or for maintenance of iron stores.

The safety and efficacy of an accelerated iron sucrose dosing regimen in patients with chronic kidney disease

An accelerated regimen of high-dose intravenous iron sucrose therapy in a cohort of iron-deficient, anemic Chronic Kidney Disease (CKD) patients was studied. Intravenous iron sucrose 500 mg was infused over three hours on two consecutive days in 107 CKD patients. Iron indices were measured at baseline and at two and seven days after completion of the iron regimen. Blood pressures were monitored immediately prior to, and hourly throughout the iron sucrose infusions. Results showed that transferrin saturation and serum ferritin increased from 18.5 ± 8.5% and 177 ± 123.8 ng/ml at baseline to 40.2 ± 22.3% and 811 ± 294.1 ng/ml in 102 evaluated patients (P < 0.015). Blood pressure rose slightly, but not significantly, throughout the
infusions, and altering the infusion rate was not necessary. It was concluded that an accelerated regimen of high-dose intravenous iron sucrose therapy in CKD patients was safe and effective in restoring iron stores, and might potentially save time and improve patient adherence.

INDICATIONS AND USAGE
Overcom™ is indicated for treatment of iron deficiency anemia in which rapid and reliable substitution of iron is required.

CONTRAINDICATIONS

- All anemias not associated with iron deficiency.
- Hypersensitivity to drug, or any of its inactive components.
- Evidence of iron overload.

WARNINGS

Hypersensitivity reactions: Potentially fatal hypersensitivity reactions characterized by cardiovascular collapse, cardiac arrest, bronchospasm, oral or pharyngeal edema, dyspnea, angioedema, urticaria, or pruritus sometimes associated with pain and muscle spasm of the chest or back have been reported rarely in patients receiving iron sucrose injection.

Flushing and hypotension: Hypotension associated with light-headedness, malaise, fatigue, weakness or severe pain in the chest, back, flanks, or groin has been associated with administration of intravenous iron. These hypotensive reactions are not associated with signs of hypersensitivity and have usually resolved within one or two hours.

PRECAUTIONS

General: Iron is not eliminated easily from the body and accumulation can be toxic. Unnecessary therapy with parenteral iron will cause excess storage of iron and consequent possibility of iatrogenic hemosiderosis. Overcom™ should not be administered in patients with iron overload.

Pregnancy: Iron sucrose injection should be used in pregnancy only if the potential benefits justify the potential risks to the fetus.

Pediatric use: Safety and effectiveness of iron sucrose in pediatric patients have not been established.

Lactation: It is not known whether iron sucrose is excreted in breast milk. Caution should be exercised when Overcom™ is administered to nursing women.

Geriatric use: There are no well controlled clinical trials evaluating the effect of iron sucrose injection in elderly population (> 65 years). Differences in responses to iron sucrose injection have not been identified in clinical studies involving both adults and elderly. Greater sensitivity of some older individuals cannot be ruled out.

NOT TO BE USED IN NEW BORN AND INFANTS.

ADVERSE REACTIONS

Adverse reactions, whether or not related to iron sucrose administration, reported by >1% of treated patients from a total of 231 patients in two studies are categorized below by body system are as follows:

- **Body as a Whole:** Headache, fever, pain, asthenia, unwell, malaise.
- **Cardiovascular Disorders, General:** Hypotension, chest pain, hypertension, hypervolemia.
- **Gastrointestinal System Disorders:** Nausea, vomiting, abdominal pain, elevated liver enzymes, diarrhea.
- **Nervous System:** Dizziness.
- **Musculoskeletal System:** Cramps/leg cramps, musculoskeletal pain.
- **Respiratory System:** Dyspnea, pneumonia, cough.
- **Skin and appendages:** Pruritus, application site reaction.
OVERDOSE AND TREATMENT
Dosages of Overcom™ in excess of iron needs may lead to accumulation of iron in storage sites leading to hemosiderosis. Periodic monitoring of iron parameters such as serum ferritin and transferrin saturation may assist in recognizing iron accumulation. Overcom™ should not be administered to patients with iron overload and should be discontinued when serum ferritin levels equal or exceed established guidelines. Particular caution should be exercised to avoid iron overload where anemia unresponsive to treatment has been incorrectly diagnosed as iron deficiency anemia.

Symptoms associated with overdosage or infusing Overcom™ too rapidly included hypotension, headache, vomiting, nausea, dizziness, joint aches, paresthesia, abdominal and muscle pain, edema, and cardiovascular collapse. Most symptoms have been successfully treated with IV fluids, hydrocortisone, and/or antihistamines. Infusing the solution as recommended or at a slower rate may also alleviate symptoms.

DOSAGE AND ADMINISTRATION
The recommended dosage of Overcom™ for the repletion treatment of iron deficiency in hemodialysis patients is 5 mL that is 100 mg of elemental iron delivered intravenously during the dialysis session. Most patients will require a minimum cumulative dose of 1,000 mg of elemental iron, administered over 10 sequential dialysis sessions, to achieve a favorable hemoglobin or hematocrit response. Patients may continue to require therapy with Overcom™ or other intravenous iron preparations at the lowest dose necessary to maintain target levels of hemoglobin, hematocrit and laboratory parameters of iron storage within acceptable limits.

The dosage can be individually adapted according to the total iron deficit calculated with the following formula:

\[
\text{Total iron deficit (mg)} = \text{bodyweight [kg]} \times ([\text{target Hb} - \text{actual Hb}] \text{ (g/l)} \times 0.24^* + \text{depot iron (mg)}
\]

30 to 35 kg bodyweight: Target Hb = 130g/l; respective depot iron = 15 mg/kg bodyweight; Over 35 kg bodyweight: Target Hb = 150g/l; respective depot iron = 500mg

*Factor 0.24 = 0.0034 x 0.07 x 1000 \{iron content of Hb \cong 0.34%; blood volume \cong 7% body weight; Factor 1000 = conversion from g to mg\}

Administration: Overcom™ must only be administered intravenously either by slow injection or by infusion. In clinical trials, Overcom™ was administered intravenously directly into the dialysis line.

Slow Intravenous Injection: In chronic renal failure patients, Overcom™ may be administered undiluted by slow intravenous injection into the dialysis line at a rate of 1 ml (20 mg iron) solution per minute (i.e. 5 minutes per ampoule) not exceeding one ampoule of Overcom™ (100 mg iron) per injection. Discard any unused portion.

Infusion: Overcom™ may also be administered by infusion (into the dialysis line for hemodialysis patients). The content of each ampoule must be diluted exclusively in a maximum of 100 mL of 0.9% NaCl, immediately prior to infusion. The solution should be infused at a rate of 100 mg of iron over a period of at least 15 minutes. Unused diluted solution should be discarded.

DRUG INTERACTIONS
Overcom™ should not be administered concomitantly with oral iron preparations since the absorption of oral iron is reduced.

NOTE: Do not mix Overcom™ with other medications or add to parenteral nutrition solutions for intravenous infusion. Parenteral drug products should be inspected visually for absence of particulate matter and discoloration prior to administration, whenever the solution and container permit.

STORAGE INSTRUCTIONS
Store at a temperature below 25°C, protect from light. Incorrect storage can lead to formation of sediments visible to the unaided eye.
REFERENCES