For the treatment of iron deficiency anemia in chronic hemodialysis patients undergoing epoetin therapy

Now Available

Nulecit™

Available in a Vial

- Convenient administration of regular low doses of IV iron with 62.5-mg single-dose vials[1]

AB-Rated by the FDA[2]

- Nulecit™ is therapeutically equivalent to branded sodium ferric gluconate complex in sucrose injection[3]

Optimized ESA Usage and Hospital Spending

- Sodium ferric gluconate complex in sucrose injection* showed a mean reduction in ESA requirements by up to 60.2%[4]
- Sodium ferric gluconate complex in sucrose injection* provided significant cost savings when used with ESA therapy[5†]
  - $1390 net cost savings per g/dL Hb increase over 12 weeks compared to ESA alone[5‡]

Stability Data Available[6]

- Data supports its stability in syringes and saline bags[6]
  - Stability testing with syringes was conducted at room temperature for up to 2 days and at refrigerated conditions for up to 7 days
  - Stability testing with intravenous infusion bags containing 0.9% sodium chloride solution was conducted at room temperature for up to 1 day and at refrigerated conditions for up to 7 days

More Than 10 Years of Clinical Use[7]

- Sodium ferric gluconate complex in sucrose injection* is safe[7] and effective[8]

* Studies used Ferrlecit®. Nulecit™ is bioequivalent to Ferrlecit®.
† In anemic patients with high ferritin (500-1200 ng/mL), low TSAT (<25%), and receiving adequate ESA therapy.
‡ Economic model only included drugs and hospitalizations due to serious adverse events. In DRIVE (Dialysis Patients' Response to IV Iron with Elevated Ferritin), patients were either given no iron (control group) or Ferrlecit® (sodium ferric gluconate in sucrose injection; 125 mg x 8); ESA dosage was raised 25% in each group at randomization with no further dose adjustments. DRIVE-II was a 6-week, observational extension of the DRIVE study designed to evaluate the sustained effects of IV iron administration on epoetin requirements, hemoglobin (Hb), and iron parameters under usual anemia clinical management. Investigators were not restricted in the type of iron product administered.

For more information, please visit Nulecit.com.

Important Safety Information

• Sodium ferric gluconate complex in sucrose is contraindicated in non iron-deficient anemias, in patients hypersensitive to sodium ferric gluconate complex in sucrose or its inactive components, or with evidence of iron overload • Hypersensitivity reactions have been reported with injectable iron products • Hypotension has been reported with rapid administration of IV iron • In a single-dose, placebo-controlled safety study (n=1097), the most frequent adverse events occurring after sodium ferric gluconate complex in sucrose administration were hypotension, nausea, and vomiting and/or diarrhea • In multiple-dose studies (n=126), the most frequent adverse events, whether or not related to sodium ferric gluconate complex in sucrose administration were nausea, vomiting and/or diarrhea, injection site pain, hypotension, cramps, hypertension, dizziness, dyspnea, and chest pain

Please see next page for references and brief summary of full Prescribing Information.

Nulecit™
(sodium ferric gluconate complex in sucrose injection) 62.5 mg/5 mL

Watson®

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References: 1. Nulecit™ full Prescribing Information, Watson Pharma, Inc. 2010. **2.** US Department of Health & Human Services, US Food and Drug Administration. Orange Book: *Approved Drug Products with Therapeutic Equivalence Evaluations* [Database]. Silver Spring, MD. http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=078215&Table1=OB_Rx. Accessed April 5, 2011. **3.** US Department of Health and Human Services, Food and Drug Administration. *Approved Drug Products with Therapeutic Equivalence Evaluations*. 31st ed. 2011. **4.** García Cortés MJ, Sánchez Perales MC, Borrego Utiel FJ, et al. Estudio de la eficacia del hierro parenteral en pacientes en hemodiálisis tratados con eritropoyetina. *Nefrologia*. 1997;17:424-429. **5.** Pizzi LT, Bunz TJ, Coyne DW, Goldfarb DS, Singh AK. Ferric gluconate treatment provides cost savings in patients with high ferritin and low transferrin saturation. *Kidney Int*. 2008;74:1588-1595. **6.** Data on file, Watson Laboratories, Inc. **7.** Michael B, Coyne DW, Fishbane S, et al. Sodium ferric gluconate complex in hemodialysis patients: adverse reactions compared to placebo and iron dextran. *Kidney Int*. 2002;61:1830-1839. **8.** Nissenson AR, Lindsay RM, Swan S, Seligman P, Strobos J. Sodium ferric gluconate complex in sucrose is safe and effective in hemodialysis patients: North American clinical trial. *Am J Kid Dis*. 1999;33:471-482.

Rx Only

Nulecit™

(sodium ferric gluconate complex in sucrose injection) *62.5 mg/5 mL*

BRIEF SUMMARY

See package insert for full Prescribing Information.

INDICATIONS AND USAGE

Nulecit™ (sodium ferric gluconate complex in sucrose injection) is indicated for treatment of iron deficiency anemia in adult patients and in pediatric patients age 6 years and older undergoing chronic hemodialysis who are receiving supplemental epoetin therapy.

CONTRAINDICATIONS

All anemias not associated with iron deficiency. Hypersensitivity to Nulecit™ or any of its inactive components. Evidence of iron overload.

WARNINGS

Hypersensitivity reactions have been reported with injectable iron products. See **PRECAUTIONS**.

PRECAUTIONS

General: Iron is not easily eliminated from the body and accumulation can be toxic. Unnecessary therapy with parenteral iron will cause excess storage of iron with consequent possibility of iatrogenic hemosiderosis. Iron overload is particularly apt to occur in patients with hemoglobinopathies and other refractory anemias. Nulecit™ should not be administered to patients with iron overload. See **OVERDOSAGE**.

Hypersensitivity Reactions: One case of a life-threatening hypersensitivity reaction was observed in 1,097 patients who received a single dose of sodium ferric gluconate complex in sucrose injection in a post-marketing safety study. In the post-marketing spontaneous reporting system, life-threatening hypersensitivity reactions have been reported rarely in patients receiving sodium ferric gluconate complex in sucrose injection. See **ADVERSE REACTIONS**.

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. Successful treatment may consist of observation or, if the hypotension causes symptoms, volume expansion. See **ADVERSE REACTIONS**.

Carcinogenesis, mutagenesis, impairment of fertility: Long term carcinogenicity studies in animals were not performed. Studies to assess the effects of sodium ferric gluconate complex in sucrose injection on fertility were not conducted. Sodium ferric gluconate complex in sucrose injection was not mutagenic in the Ames test and the rat micronucleus test. It produced a clastogenic effect in an *in vitro* chromosomal aberration assay in Chinese hamster ovary cells.

Pregnancy Category B: Sodium ferric gluconate complex in sucrose injection was not teratogenic at doses of elemental iron up to 100 mg/kg/day (300 mg/m^2/day) in mice and 20 mg/kg/day (120 mg/m^2/day) in rats. On a body surface area basis, these doses were 1.3 and 3.24 times the recommended human dose (125 mg/day or 92.5 mg/m^2/day) for a person of 50 kg body weight, average height and body surface area of 1.46 m^2. There were no adequate and well-controlled studies in pregnant women. Nulecit™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Nulecit™ is administered to a nursing woman.

Pediatric Use: Sodium ferric gluconate complex in sucrose injection was shown to be safe and effective in pediatric patients ages 6 to 15 years (refer to **CLINICAL STUDIES** section). Safety and effectiveness in pediatric patients younger than 6 years of age have not been established.

Nulecit™ contains benzyl alcohol and therefore should not be used in neonates.

Geriatric Use: Clinical studies of sodium ferric gluconate complex in sucrose injection did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In particular, 51/159 hemodialysis patients in North American clinical studies were aged 65 years or older. Among these patients, no differences in safety or efficacy as a result of age were identified. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Exposure to sodium ferric gluconate complex in sucrose injection has been documented in over 1,400 patients on hemodialysis. This population included 1,097 sodium ferric gluconate complex in sucrose injection-naïve patients who received a single-dose of sodium ferric gluconate complex in sucrose injection in a placebo-controlled, cross-over, post-marketing safety study. Undiluted sodium ferric gluconate complex in sucrose injection was administered over ten minutes (125 mg of elemental iron at 12.5 mg/min). No test dose was used. From a total of 1,498 sodium ferric gluconate complex in sucrose injection-treated patients in medical reports, North American trials, and post-marketing studies, twelve patients (0.8%) experienced serious reactions which precluded further therapy with sodium ferric gluconate complex in sucrose injection.

Hypersensitivity Reactions: See **PRECAUTIONS**. In the single-dose, post-marketing, safety study one patient experienced a life-threatening hypersensitivity reaction (diaphoresis, nausea, vomiting, severe lower back pain, dyspnea, and wheezing for 20 minutes) following sodium ferric gluconate complex in sucrose injection administration. Among 1,097 patients who received sodium ferric gluconate complex in sucrose injection in this study, there were 9 patients (0.8%) who had an adverse reaction that, in the view of the investigator, precluded further sodium ferric gluconate complex in sucrose injection administration (drug intolerance). These included one life-threatening reaction, six allergic reactions (pruritus x 2, facial flushing, chills, dyspnea/chest pain, and rash), and two other reactions (hypotension and nausea). Another 2 patients experienced (0.2%) allergic reactions not deemed to represent drug intolerance (nausea/malaise and nausea/dizziness) following sodium ferric gluconate complex in sucrose injection administration.

Seventy-two (7.0%) of the 1,034 patients who had prior iron dextran exposure had a sensitivity to at least one form of iron dextran (INFeD® or Dexferrum®). The patient who experienced a life-threatening adverse event following sodium ferric gluconate complex in sucrose injection administration during the study had a previous severe anaphylactic reaction to dextran in both forms (INFeD® and Dexferrum®). The incidences of both drug intolerance and suspected allergic events following first dose sodium ferric gluconate complex in sucrose injection administration were 2.8% in patients with prior iron dextran sensitivity compared to 0.8% in patients without prior iron dextran sensitivity.

In this study, 28% of the patients received concomitant angiotensin converting enzyme inhibitor (ACEi) therapy. The incidences of both drug intolerance or suspected allergic events following first dose sodium ferric gluconate complex in sucrose injection administration were 1.6% in patients with concomitant ACEi use compared to 0.7% in patients without concomitant ACEi use. The patient with a life-threatening event was not on ACEi therapy. One patient had facial flushing immediately on sodium ferric gluconate complex in sucrose injection exposure. No hypotension occurred and the event resolved rapidly and spontaneously without intervention other than drug withdrawal.

In multiple dose Studies A and B, no fatal hypersensitivity reactions occurred among the 126 patients who received sodium ferric gluconate complex in sucrose injection. Sodium ferric gluconate complex in sucrose injection-associated hypersensitivity events in Study A resulting in premature study discontinuation occurred in three out of a total 88 (3.4%) sodium ferric gluconate complex in sucrose injection-treated patients. The first patient withdrew after the development of pruritus and chest pain following the test dose of sodium ferric gluconate complex in sucrose injection. The second patient, in the high-dose group, experienced nausea, abdominal and flank pain, fatigue and rash following the first dose of sodium ferric gluconate complex in sucrose injection. The third patient, in the low-dose group, experienced a "red blotchy rash" following the first dose of sodium ferric gluconate complex in sucrose injection. Of the 38 patients exposed to sodium ferric gluconate complex in sucrose injection in Study B, none reported hypersensitivity reactions.

Many chronic renal failure patients experience cramps, pain, nausea, rash, flushing, and pruritus.

In the postmarketing spontaneous reporting system, life-threatening hypersensitivity reactions have been reported rarely in patients receiving sodium ferric gluconate complex in sucrose injection.

Hypotension: See **PRECAUTIONS**. In the single dose safety study, post-administration hypotensive events were observed in 22/1,097 patients (2%) following sodium ferric gluconate complex in sucrose injection administration. Hypotension has also been reported following administration of sodium ferric gluconate complex in sucrose injection in European case reports. Of the 226 renal dialysis patients exposed to sodium ferric gluconate complex in sucrose injection and reported in the literature, 3 (1.3%) patients experienced hypotensive events, which were accompanied by flushing in two. All completely reversed after one hour without sequelae. Transient hypotension may occur during dialysis. Administration of Nulecit™ may augment hypotension caused by dialysis.

Among the 126 patients who received sodium ferric gluconate complex in sucrose injection in Studies A and B, one patient experienced a transient decreased level of consciousness without hypotension. Another patient discontinued treatment prematurely because of dizziness, lightheadedness, diplopia, malaise, and weakness without hypotension that resulted in a 3 to 4 hour hospitalization for observation following drug administration. The syndrome resolved spontaneously.

Adverse Laboratory Changes: No differences in laboratory findings associated with sodium ferric gluconate complex in sucrose injection were reported in North American clinical trials when normalized against a National Institute of Health database on laboratory findings in 1,100 hemodialysis patients.

Most Frequent Adverse Reactions: In the single-dose, post-marketing safety study, 11% of patients who received sodium ferric gluconate complex in sucrose injection and 9.4% of patients who received placebo reported adverse reactions. The most frequent adverse reactions following sodium ferric gluconate complex in sucrose injection were: hypotension (2%), nausea, vomiting and/or diarrhea (2%), pain (0.7%), hypertension (0.6%), allergic reaction (0.5%), chest pain (0.5%), pruritus (0.5%), and back pain (0.4%). Similar adverse reactions were seen following placebo administration. However, because of the high baseline incidence of adverse events in the hemodialysis patient population, insufficient number of exposed patients, and limitations inherent to the cross-over, single dose study design, no comparison of event rates between sodium ferric gluconate complex in sucrose injection and placebo treatments can be made.

In multiple-dose Studies A and B, the most frequent adverse reactions following sodium ferric gluconate complex in sucrose injection were:

Body as a Whole: injection site reaction (33%), chest pain (10%), pain (10%), asthenia (7%), headache (7%), abdominal pain (6%), fatigue (6%), fever (5%), malaise, infection, abscess, back pain, chills, rigors, arm pain, carcinoma, flu-like syndrome, sepsis.

Nervous System: cramps (25%), dizziness (13%), paresthesias (6%), agitation, somnolence.

Respiratory System: dyspnea (11%), coughing (6%), upper respiratory infections (6%), rhinitis, pneumonia.

Cardiovascular System: hypotension (29%), hypertension (13%), syncope (6%), tachycardia (5%), bradycardia, vasodilatation, angina pectoris, myocardial infarction, pulmonary edema.

Gastrointestinal System: nausea, vomiting and/or diarrhea (35%), anorexia, rectal disorder, dyspepsia, eructation, flatulence, gastrointestinal disorder, melena.

Musculoskeletal System: leg cramps (10%), myalgia, arthralgia.

Skin and Appendages: pruritus (6%), rash, increased sweating.

Genitourinary System: urinary tract infection.

Special Senses: conjunctivitis, abnormal vision, ear disorder.

Metabolic and Nutritional Disorders: hyperkalemia (6%), generalized edema (5%), leg edema, peripheral edema, hypoglycemia, edema, hypervolemia, hypokalemia.

Hematologic System: abnormal erythrocytes (11%), anemia, leukocytosis, lymphadenopathy.

Other Adverse Reactions Observed During Clinical Trials: In the single-dose post-marketing safety study in 1,097 patients receiving sodium ferric gluconate complex in sucrose injection, the following additional events were reported in two or more patients: hypertonia, nervousness, dry mouth, and hemorrhage.

Pediatric Patients: In a clinical trial of 66 iron-deficient pediatric hemodialysis patients, 6 to 15 years of age, inclusive, who were receiving a stable erythropoietin dosing regimen, the most common adverse events, whether or not related to study drug, occurring in ≥ 5%, regardless of treatment group, were: hypotension (35%), headache (24%), hypertension (23%), tachycardia (17%), vomiting (11%), fever (9%), nausea (9%), abdominal pain (9%), pharyngitis (9%), diarrhea (8%), infection (8%), rhinitis (6%), and thrombosis (6%). More patients in the higher dose group (3.0 mg/kg) than in the lower dose group (1.5 mg/kg) experienced the following adverse events: hypotension (41% vs. 28%), tachycardia (21% vs. 13%), fever (15% vs. 3%), headache (29% vs. 19%), abdominal pain (15% vs. 3%), nausea (12% vs. 6%), vomiting (12% vs. 9%), pharyngitis (12% vs. 6%), and rhinitis (9% vs. 3%).

Postmarketing Surveillance: The following additional adverse reactions have been identified with the use of sodium ferric gluconate complex in sucrose injection from postmarketing spontaneous reports: dysgeusia, hypoesthesia, loss of consciousness, convulsion, skin discoloration, pallor, phlebitis, and shock. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

OVERDOSAGE

Dosages in excess of iron needs may lead to accumulation of iron in iron storage sites and hemosiderosis. Periodic monitoring of laboratory parameters of iron storage may assist in recognition of iron accumulation. Nulecit™ should not be administered in patients with iron overload.

Serum iron levels greater than 300 mcg/dL may indicate iron poisoning which is characterized by abdominal pain, diarrhea, or vomiting which progresses to pallor or cyanosis, lassitude, drowsiness, hyperventilation due to acidosis, and cardiovascular collapse. Caution should be exercised in interpreting serum iron levels in the 24 hours following the administration of Nulecit™ since many laboratory assays will falsely overestimate serum or transferrin bound iron by measuring iron still bound to the Nulecit™ complex. Additionally, in the assessment of iron overload, caution should be exercised in interpreting serum ferritin levels in the week following Nulecit™ administration since, in clinical studies, serum ferritin exhibited a non-specific rise which persisted for five days.

The Nulecit™ iron complex in sucrose injection is not dialyzable.

Sodium ferric gluconate complex in sucrose injection at elemental iron doses of 125 mg/kg, 78.8 mg/kg, 62.5 mg/kg and 250 mg/kg caused deaths to mice, rats, rabbits, and dogs respectively. The major symptoms of acute toxicity were decreased activity, staggering, ataxia, increases in the respiratory rate, tremor, and convulsions.

Individual doses exceeding 125 mg may be associated with a higher incidence and/or severity of adverse events based on information from postmarketing spontaneous reports. These adverse events included hypotension, nausea, vomiting, abdominal pain, diarrhea, dizziness, dyspnea, urticaria, chest pain, paresthesta, and peripheral swelling. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

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