HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TRIFERIC AVNU safely and effectively. See full prescribing information for TRIFERIC AVNU.

TRIFERIC AVNU ® (ferric pyrophosphate citrate injection), for intravenous use

Initial U.S. Approval: 2015

----------INDICATIONS AND USAGE----------

Triferic AVNU is an iron replacement product indicated for the replacement of iron to maintain hemoglobin in adult patients with hemodialysis-dependent chronic kidney disease (HDD-CKD). (1)

Limitations of Use

- Triferic AVNU is not intended for use in patients receiving peritoneal dialysis. (1)
- Triferic AVNU has not been studied in patients receiving home hemodialysis (1)

----------DOSAGE AND ADMINISTRATION----------

6.75 mg iron (III)_intravenously over 3 to 4 hours at each hemodialysis session via pre-dialyzer infusion line, post-dialyzer infusion line, or a separate connection to the venous blood line. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

Injection: 6.75 mg iron (III) per 4.5 mL solution (1.5 mg iron (III) per mL) in single-dose luer lock ampule (3)

----------CONTRAINDICATIONS----------

None.

----------WARNINGS AND PRECAUTIONS----------

Hypersensitivity Reactions: Observe for signs and symptoms of hypersensitivity during and after hemodialysis and until clinically stable. (5.1)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence ≥3%) are: headache, peripheral edema, asthenia, AV fistula thrombosis, urinary tract infection, AV fistula site hemorrhage, pyrexia, fatigue, procedural hypotension, muscle spasms, pain in extremity, back pain, and dyspnea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Rockwell Medical at 1-855-333-4315 or 1-248-960-9009 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

See 17 for PATIENT COUNSELING INFORMATION.

Revised: [3/2020]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Triferic is an iron replacement product indicated for the replacement of iron to maintain hemoglobin in adult patients with hemodialysis-dependent chronic kidney disease (HDD-CKD).

Limitations of Use

- Triferic is not intended for use in patients receiving peritoneal dialysis.
- Triferic has not been studied in patients receiving home hemodialysis.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage of Triferic AVNU is 6.75 mg iron (III) undiluted as a slow continuous intravenous infusion over 3 to 4 hours via the pre-dialyzer infusion line, post-dialyzer infusion line, or via a separate connection to the venous blood line during hemodialysis.

Administer Triferic AVNU at each dialysis procedure for as long as patients are receiving maintenance hemodialysis therapy for CKD.

The dosage of Triferic AVNU solution is expressed as mg of iron (III). Each mL of Triferic AVNU injection for intravenous administration contains 1.5 mg iron as iron (III).

2.2 Preparation and Administration

Each ampule of Triferic AVNU is intended for single-use only.

Use aseptic technique to prepare Triferic AVNU as follows:

- Visually inspect Triferic AVNU solution for signs of precipitation prior to use. The solution should be clear and slightly yellow-green in color.
- Holding the top of the ampule, shake with one single downward movement in order to remove the solution remaining in the cap.
- To open, twist the ampule body and the ampule head in opposite directions until the neck breaks off the top.
- Attach a 10 mL or 20 mL luer-lock syringe to the ampule and withdraw the contents (6.75 mg in 4.5 mL).
- Connect the syringe to the attached pre-dialyzer infusion line, post-dialyzer infusion line, or to a separate connection to the venous blood line.
- Mount the syringe on an infusion pump and administer as a slow continuous infusion of Triferic AVNU (4.5 mL) over 3 to 4 hours.
- Discard unused portion.

3 DOSAGE FORMS AND STRENGTHS

Injection: 6.75 mg iron (III) per 4.5 mL (1.5 mg iron (III) per mL) clear slightly yellow-green solution in single-dose luer lock ampule.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Serious hypersensitivity reactions, including anaphylactic-type reactions, some of which have been life-threatening and fatal, have been reported in patients receiving parenteral iron products. Patients may present with shock, clinically significant hypotension, loss of consciousness, and/or collapse. Monitor patients for signs and symptoms of hypersensitivity during and after hemodialysis until clinically stable. Personnel and therapies should be immediately available for the treatment of serious hypersensitivity reactions. [*see Adverse Reactions (6.1)*]

Hypersensitivity reactions have been reported in 1 (0.3%) of 292 patients receiving ferric pyrophosphate citrate in two randomized clinical trials.

5.2 Iron Laboratory Testing

Determine iron status on pre-dialysis blood samples. Post-dialysis serum iron parameters may overestimate serum iron and transferrin saturation.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described below and elsewhere in the labeling:

- Hypersensitivity Reactions. [*see Warnings and Precautions (5.1)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug may not reflect the rates observed in practice.

The safety of ferric pyrophosphate citrate injection, for intravenous use, has been established based on adequate and well-controlled studies of ferric pyrophosphate citrate solution for hemodialysis [*see Clinical Studies (14)*]. Below is a display of the adverse reactions of ferric pyrophosphate citrate solution for hemodialysis in these adequate and well-controlled studies.

The safety of ferric pyrophosphate citrate solution for hemodialysis was evaluated in 292 patients in two randomized, placebo-controlled clinical trials (CRUISE 1 (NCT01320202) and CRUISE 2 (NCT01322347)) who were administered ferric pyrophosphate citrate solution for hemodialysis use for periods of up to 1 year [*see Clinical Studies (14)*]. The mean total exposure

in the randomized treatment period was 5 months. A total of 296 patients received placebo treatment for a similar time period. In the two studies, 64% were male and 54% were Caucasian. The median age of patients was 60 years (range, 20 to 89 years).

Adverse reactions occurring in 3% or greater of patients treated with ferric pyrophosphate citrate solution for hemodialysis use in the randomized clinical trials are listed in Table 1.

Table 1: **Adverse Reactions Reported in CRUISE1 and CRUISE 2 in at Least 3% of Patients Receiving Ferric Pyrophosphate Citrate Solution for Hemodialysis Use and at an Incidence at Least 1% Greater than Placebo**

Body System **Adverse Reaction**	**Ferric Pyrophosphate Citrate Solution for Hemodialysis Use N=292 n (%)**	**Placebo N=296 n (%)**
Number of patients with at least one adverse reaction	229 (78)	223 (75)
General Disorders and Administration Site Conditions		
Peripheral edema	20 (7)	11 (4)
Pyrexia	13 (5)	9 (3
Asthenia	12 (4)	9 (3)
Fatigue	11 (4)	6 (2)
Infections and Infestations		
Urinary tract infection	13 (5)	4 (1)
Injury, Poisoning, and Procedural Complications		
Procedural hypotension	63 (22)	57 (19)
Arteriovenous fistula thrombosis	10 (3)	6 (2)
Arteriovenous fistula site hemorrhage	10 (3)	5 (2)
Musculoskeletal and Connective Tissue Disorders		
Muscle spasms	28 (10)	24 (8)
Pain in extremity	20 (7)	17 (6)
Back pain	13 (5)	10 (3)
Nervous System Disorders		
Headache	27 (9)	16 (5)
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnea	17 (6)	13 (4)

Other Adverse Reactions

Less common adverse reactions occurring at a frequency of <3%:

- Hypersensitivity reactions (0.3%)

Adverse Reactions Leading to Treatment Discontinuation

In clinical trials, adverse reactions leading to treatment discontinuation included headache, asthenia, dizziness, constipation, nausea, hypersensitivity reactions, intradialytic hypotension, pruritus, and pyrexia.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on Triferic AVNU use in pregnant women to inform a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. In animal reproduction studies, intravenous administration of ferric pyrophosphate citrate to pregnant rats and rabbits during organogenesis caused adverse developmental outcomes at maternally toxic dose levels that were higher than the maximum theoretical amount of iron transferred to patients from Triferic AVNU *(see Data).*

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In a fertility and early embryonic development study in female rats, the maternally toxic ferric pyrophosphate citrate dose of 40 mg/kg administered three times per week by intravenous infusion was not toxic to the developing embryo.

In embryo-fetal developmental toxicity studies, ferric pyrophosphate citrate was administered during the period of organogenesis as a one-hour intravenous infusion to pregnant rats and rabbits. No maternal or developmental toxicity was observed at doses up to 30 mg/kg/day in rats and 20 mg/kg/day in rabbits. Maternally toxic doses affected embryo-fetal development, resulting in post-implantation loss due to early resorptions, abnormal placentae, decreased fetal body weight and fetal head and vertebral malformations at 90 mg/kg/day in rats and vertebral malformations at 40 mg/kg/day in rabbits.

A pre-and post-natal development study was conducted in pregnant rats with intravenous doses of ferric pyrophosphate citrate up to 90 mg/kg/day. The maternally toxic dose of 90 mg/kg/day resulted in reductions in the number of live offspring and lower offspring body weights. There were no adverse effects on survival of offspring at doses up to 30 mg/kg/day, or on behavior, sexual maturation or reproductive parameters of offspring at any dose level.

8.2 Lactation

Risk Summary

There are no data on the presence of ferric pyrophosphate citrate in human milk, the effects on the breastfed child, or the effect on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Triferic AVNU and any potential adverse effects on the breastfed child from Triferic AVNU or from the underlying maternal condition.

8.4 Pediatric Use

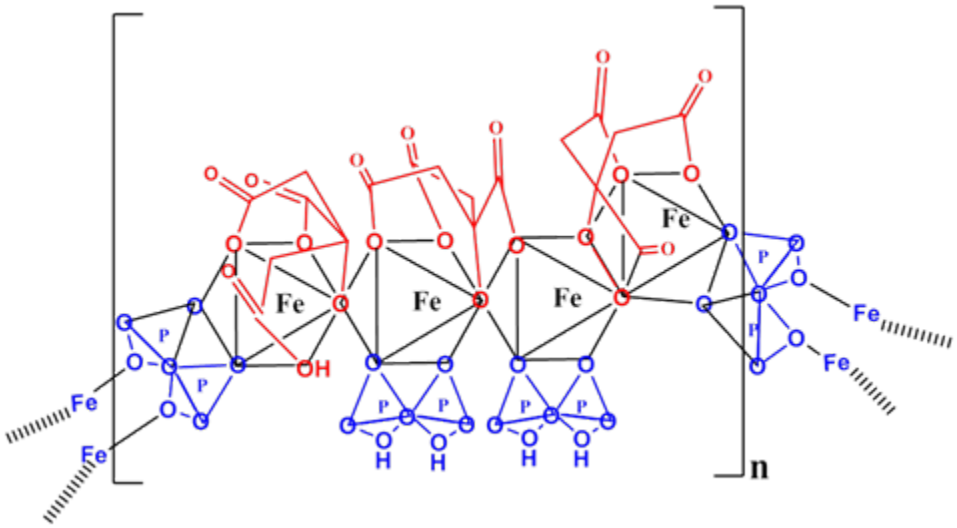
Safety and effectiveness have not been established in pediatric patients.

8.5 Geriatric Use

In controlled clinical trials, 99 (29%) patients ≥ 65 years of age were treated with ferric pyrophosphate citrate. No overall differences in safety and efficacy were observed between older and younger patients in these trials [*see Clinical Studies (14)*].

11 DESCRIPTION

Triferic AVNU (ferric pyrophosphate citrate), an iron replacement product, is a mixed-ligand iron complex in which iron (III) is bound to pyrophosphate and citrate. It has a molecular formula of $Fe_4(C_6H_4O_7)_3(H_2P_2O_7)_2(P_2O_7)$ and a relative molecular weight of approximately 1313 daltons. Ferric pyrophosphate citrate has the following structure:



Triferic AVNU (ferric pyrophosphate citrate) injection is a clear, slightly yellow-green color sterile solution containing 6.75 mg of elemental iron (III) per 4.5 mL (1.5 mg iron (III) per mL) filled in a 5 mL low density polyethylene (LDPE) luer-lock ampule. Each Triferic AVNU ampule contains iron (0.14-0.17 % w/w), and less than 0.1% w/w citrate, pyrophosphate, phosphate, sodium and sulfate. One Triferic AVNU ampule is administered directly into the pre-dialyzer infusion line, post-dialyzer infusion line, or to a separate connection to the venous blood line over 3 to 4 hours.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Triferic AVNU contains iron in the form of ferric pyrophosphate citrate. Iron binds to transferrin for transport to erythroid precursor cells to be incorporated into hemoglobin.

12.2 Pharmacodynamics

Ferric pyrophosphate citrate exposure-response relationships and the time course of pharmacodynamics response are unknown.

Drug interaction Studies

In vitro studies showed that ferric pyrophosphate citrate did not impact the pharmacodynamics of unfractionated heparin or low molecular weight heparin.

12.3 Pharmacokinetics

Following administration of ferric pyrophosphate citrate 6.75 mg via a 3-hour intravenous infusion at a rate of 1.5 mg/hr (6.5 mg delivered), the total plasma iron and transferrin bound iron exposure values are provided in Table 2.

Table 2: Total Plasma Iron and Transferrin Bound Iron Exposure Parameters after Intravenous Administration of Ferric Pyrophosphate Citrate via the Pre-dialyzer and Post-dialyzer Infusion line during Hemodialysis.

Plasma Analyte	**PK Parameter**	**Ferric pyrophosphate citrate**	
		pre-dialyzer infusion line (N=26)	**post-dialyzer infusion line (N=25)**
Total Plasma Iron	C_{max} (µg/dL)	170 (24%)	164 (23%)
	$AUC_{0\text{-}tlast}$ (µg.h/dL)	1260 (35%)	1230 (33%)
*Transferrin bound iron	C_{max} (µg/dL)	180 (24%)	169 (28%)
	$AUC_{0\text{-}tlast}$ (µg.h/dL)	1250 (37%)	1190 (46%)

*N=17 for pre-dilayzer and N=16 for post-dialyzer

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies examining the carcinogenic potential of ferric pyrophosphate citrate have not been conducted.

Ferric pyrophosphate citrate was clastogenic in the *in vitro* chromosomal aberration assay in CHO cells in the presence of metabolic activation. Ferric pyrophosphate citrate was not mutagenic in the *in vitro* bacterial reverse mutation (Ames) test or clastogenic in the *in vitro* chromosomal aberration assay in CHO cells in the absence of metabolic activation or in the *in vivo* mouse micronucleus assay.

In a combined male and female fertility study in rats, ferric pyrophosphate citrate was administered intravenously over one hour three times per week at doses of up to 40 mg/kg. No adverse effects on fertility or reproduction were noted.

14 CLINICAL STUDIES

The efficacy of Triferic AVNU has been established based on adequate and well-controlled adult studies of ferric pyrophosphate citrate in iron replacement in patients with hemodialysis-dependent chronic kidney disease (HDD-CKD). Below is a display of the results of the adequate and well-controlled studies of ferric pyrophosphate citrate in this condition.

The efficacy of ferric pyrophosphate citrate in patients with HDD-CKD was assessed in two randomized, single blind, placebo-controlled clinical trials. Patients with hemoglobin of 9 g/dL to 12 g/dL with TSAT > 20% and serum ferritin concentrations > 200 mcg/L were enrolled. Patients were to remain in randomized treatment until pre-specified hemoglobin or ferritin criteria were met, indicating the need for a change in anemia management or if they completed 48 weeks. Ferric pyrophosphate citrate was added to bicarbonate concentrate with a final concentration of 110 mcg iron/L in the dialysate and was administered 3 or 4 times per week during hemodialysis. Most patients were receiving stable dose of erythropoiesis stimulating agents (ESAs) at baseline. After randomization, patients' ESA doses were not to be changed.

In CRUISE 1 (NCT01320202), the mean age of patients was 58 years (range 23 to 89); 68% were male, 55% were Caucasian, 32% were African American, and 13% were other races.

In CRUISE 2 (NCT01322347), the mean age of patients was 58 years (range 20 to 89); 59% were male, 54% were Caucasian, 40% were African American, and 6% were other races.

Efficacy was assessed by the mean change in hemoglobin from baseline to the end-of-treatment period (average hemoglobin of the last one-sixth (1/6th) of the time in the randomized treatment period). About 18% of patients completed the planned 48 week treatment duration.

Table 3 shows the mean changes in hemoglobin (Hgb) and iron parameters in each treatment group from baseline to the end-of-treatment period for the ITT population.

Table 3: Changes from Baseline to End of Treatment in Hemoglobin, Ferritin, Reticulocyte Hgb (CHr), and Transferrin Saturation (TSAT).

	CRUISE 1		CRUISE 2	
	Ferric pyrophosphate citrate n=152	Placebo n=153	Ferric pyrophosphate citrate n=147	Placebo n=147
Baseline Hemoglobin Mean ± SD, g/dL	10.96 (0.592)	10.91 (0.632)	10.96 (0.605)	10.94 (0.622)
Hemoglobin Change from Baseline to End-of-Treatment Period Mean ± SD g/dL	-0.03 (1.147)†	-0.38 (1.240)	-0.08 (1.152)†	-0.44 (1.157)
Baseline Ferritin Mean (SD), mcg/L	508.2 (193.55)	509.3 (209.06)	519.0 (201.56)	478.4 (200.59)
Ferritin, Change from Baseline to End-of-Treatment Mean (SD), mcg/L	-70.8 (132.41)	-141 .2 (187.74)	-65.3 (162.45)	-120.9 (268.19)
Baseline Reticulocyte Hemoglobin (CHr) Mean (SD), pg	32.37 (1.967)	32.53 (1.965)	32.56 (2.210)	32.57 (1.932)
CHr, Change from Baseline to End-of-Treatment Mean (SD), pg	-0.22 (1.191)	-0.90 (1.407)	-0.55 (1.441)	-0.85 (1.474)
Baseline TSAT Mean (SD), %	28.2 (8.23)	27.1 (7.76)	28.0 (8.15)	28.2 (8.52)
TSAT, Change from Baseline to End-of-Treatment) Mean (SD), %	-1.0 (9.07)	-2.9 (7.65)	-0.9 (7.54)	-3.6 (7.29)

† $p < 0.05$

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Triferic AVNU injection is a clear to slightly yellow-green solution available in single-dose luer lock ampules in the following package sizes:

NDC Code	Package Description	Amount/Total Volume (per ampule)
NDC 57278-318-01	10 Luer-lock ampules per pouch	6.75 mg iron (III)/4.5 mL (1.5 mg iron (III) per mL)
NDC 57278-318-02	4 Pouches per Carton	

16.2 Storage

Store ampules protected from light in the aluminum pouch at controlled room temperature (20° to 25°C [68° to 77°F]); excursions permitted to 15°-30°C (59° to 86°F) [See USP Controlled

Room Temperature]. Do not freeze.

17 PATIENT COUNSELING INFORMATION

Prior to the administration of Triferic AVNU:

- Question patients regarding any prior history of reactions to parenteral iron products.
- Advise patients of the risk of hypersensitivity reactions associated with Triferic AVNU.
- Advise patient to report any signs and symptoms of hypersensitivity that may develop during and after the dialysis session, such as rash, itching, dizziness, lightheadedness, swelling and breathing problems [*see Warnings and Precautions (5)*].

Manufactured for
Rockwell Medical, Inc.
30142 S Wixom Rd
Wixom, MI 48393