



Luis Caveda
Senior Director of Regulatory Affairs
Rockwell Medical, Inc
30142 South Wixom Road
Wixom, MI 48393

RE: NDA 206317; NDA 208551

TRIFERIC[®] (ferric pyrophosphate citrate) solution and TRIFERIC[®] (ferric pyrophosphate citrate) powder packet for addition to bicarbonate concentration
MA 26; MA 22

Dear Mr. Caveda:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed the Rockwell Medical, Inc's (Rockwell Medical) webpage¹ titled, "Triferic[®]" (webpage) under the "Therapeutic Focus" tab for TRIFERIC[®] (ferric pyrophosphate citrate) solution and powder packet for addition to bicarbonate concentration (Triferic). The webpage is false or misleading in that it presents information about the benefits of Triferic but fails to include **any** risk information about the drug, makes false or misleading claims and/or representations about the risks and efficacy associated with Triferic, and omits other material facts. Thus, the webpage misbrands Triferic within the meaning of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and makes its distribution violative. 21 U.S.C. 352(a), (n); 321(n); 331(a). See 21 CFR 202.1(e)(3)(ii); 202.1(e)(5). These violations are concerning from a public health perspective because patients with hemodialysis-dependent chronic kidney disease (HDD-CKD) are a vulnerable patient population at increased risk of medical complications and adverse outcomes.

Background

Below are the indication and summary of the most serious and most common risks associated with the use of Triferic.² According to the FDA-approved product labeling (PI)³ (emphasis original):

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

¹ <https://www.rockwellmed.com/bio-pharma-development/triferic/> (last accessed November 18, 2019).

² This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional piece(s) cited in this letter.

³ The version of the Triferic PI referred to in this letter was approved on March 28, 2018.

Triferic is not intended for use in patients receiving peritoneal dialysis.

Triferic has not been studied in patients receiving home hemodialysis.

The PI contains warnings and precautions regarding hypersensitivity reactions and iron laboratory testing. In addition, the PI indicates that the most common adverse reactions associated with Triferic 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.

False or Misleading Risk and Benefit Presentations

Promotional materials misbrand a drug if they are false or misleading with respect to risk or benefits. The determination of whether promotional materials are misleading includes, among other things, not only representations made or suggested in promotional materials, but also failure to reveal facts that are material in light of the representations made by the materials or with respect to consequences that may result from the use of the drug as recommended or suggested in the materials.

The webpage contains claims and/or representations about the benefits of Triferic but fails to communicate **any** risk information about the product. By omitting the risks associated with Triferic, the webpage fails to provide material information about the consequences that may result from the use of the drug and creates a misleading impression about the safety of Triferic.

The webpage makes claims such as the following:

- Unlike current nurse IV iron administration, Triferic is seamlessly administered via dialysate directly to the bone marrow, delivering iron in a physiologic manner avoiding iron storage in the liver or reticuloendothelial system.
- Triferic improves the effectiveness of iron delivery for the majority of dialysis patients and prevents iron induced liver damage, especially for those patients with known concomitant liver disease.
- Released clinical trial data along with real world usage have shown that small, frequent doses of Triferic, as compared to the current administration of large, infrequent doses of IV iron, is safer and more effective in delivering and maintaining optimal iron balance.

These claims are misleading because they suggest Triferic is safer and more effective than other IV iron replacement products, when this has not been demonstrated. No references were cited to support these claims, and FDA is not aware of data to support claims that Triferic is safer or more effective compared to other IV iron replacement products. While we acknowledge that Triferic is the only FDA-approved iron replacement product administered via hemodialysate, once inside the blood stream, iron delivered by Triferic is used by the body in the same manner as other currently approved iron replacement products. Furthermore, with respect to claims comparing Triferic to other IV iron products regarding iron storage in the liver, we note that liver iron testing was not performed as part of routine clinical status testing in the studies supporting the approval of Triferic. These studies were also

neither designed to assess the benefit of Triferic in patients with known concomitant liver disease nor sized to quantitatively evaluate the risk of hepatotoxicity compared to IV iron. If you have data to support any of the above claims, please submit such data to FDA.

Omission of Material Facts

In addition, the webpage is misleading because it fails to provide material information regarding Triferic's full FDA-approved indication, including important limitations of use. Specifically, the INDICATIONS AND USAGE section of the PI states the following (underlined emphasis added; bolded emphasis in original):

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).

Limitation of Use

Triferic is not intended for use in patients receiving peritoneal dialysis.

Triferic has not been studied in patients receiving home hemodialysis.

By failing to adequately disclose the full indication and limitations of use associated with Triferic, the webpage creates a misleading impression about the FDA-approved indication for Triferic. This is particularly concerning given claims made on the webpage such as "Triferic improves the effectiveness of iron delivery for the majority of dialysis patients. . ." (emphasis added). This broad claim suggests that Triferic is indicated for patients receiving any type of dialysis, when it is not intended for use in patients receiving peritoneal dialysis and its safety and effectiveness for use in patients receiving home hemodialysis have not been studied.

Conclusion and Requested Action

For the reasons discussed above, the webpage misbrands Triferic within the meaning of the FD&C Act and makes its distribution violative. 21 U.S.C. 352(a), (n); 321(n); 331(a); see 21 CFR 202.1(e)(3)(ii); 202.1(e)(5).

OPDP requests that Rockwell Medical, Inc immediately cease violating the FD&C Act, as discussed above. Please submit a written response to this letter on or before December 3, 2019, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Triferic that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials. If you believe that your products are not in violation of the FD&C Act, include your reasoning and any supporting information for our consideration.

Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266**. A courtesy copy can be sent by facsimile to (301) 847-8444. To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g. a sticker) to indicate that the submission is intended for OPDP. Please refer to MA 26 and MA 22 in addition to the

NDA numbers in all future correspondence relating to this particular matter. All correspondence should include a subject line that clearly identifies the submission as a Response to Untitled Letter.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Triferic comply with each applicable requirement of the FD&C Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Robert Nguyen, PharmD
Regulatory Review Officer
Division of Advertising & Promotion Review 1
Office of Prescription Drug Promotion

{See appended electronic signature page}

Susannah O'Donnell, MPH, RAC
Team Leader
Division of Advertising & Promotion Review 1
Office of Prescription Drug Promotion

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ROBERT L NGUYEN
11/18/2019 02:27:04 PM

SUSANNAH O'DONNELL
11/18/2019 02:39:23 PM