CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208551Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 208551 SUPPL # HFD # 161

Trade Name: Triferic

Generic Name: Ferric Pyrophosphate Citrate

Applicant Name: Rockwell Medical, Inc.

Approval Date: April 25, 2016

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☐ NO ☒

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

The Application provided for new CMC information to support a new dosage form of Triferic (powder packet). NDA 206317, Triferic (solution) as ampules was approved January 23, 2015.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

c) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

d) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 206317

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the

answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☒

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # YES ☐ ! NO ☐
! Explain:

Investigation #2 !
!
IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Kimberly Scott
Title: Regulatory Project Manager
Date: April 26, 2016

Name of Office/Division Director signing form: Ann T. Farrell, MD
Title: Division of Hematology Products, Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KIMBERLY L SCOTT
04/26/2016

ANN T FARRELL
04/26/2016

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 208551 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Triferic Established/Proper Name: ferric pyrophosphate citrate Dosage Form: Powder		Applicant: Rockwell Medical, Inc. Agent for Applicant (if applicable):
RPM: Kimberly Scott		Division: Hematology Products (DHP)

NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is April 25, 2016	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: CST SharePoint)

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☐ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
Copies of all action letters *(including approval letter with final labeling)*	Approval: 4/25/16
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	
❖ Labeling reviews *(indicate dates of reviews)*	RPM: 9/3/2015 DMEPA: 1/19/2016 and 11/13/2015 DMPP/PLT (DRISK): ☒ None OPDP: 2/16/16 SEALD: ☒ None CSS: ☒ None Product Quality ☒ None Other: ☒ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	8/20/15 ☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC February 24, 2016 If PeRC review not necessary, explain:	Pediatric Record: Pediatric Page
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)*	4/22/16, 4/8/16, 4/6/16 (2) 3/25/16, 3/24/16, 3/10/16, 3/9/16 2/9/2016, 1/21/16, 1/20/16, 12/28/15, 11/19/15 10/2/15, 9/10/15 9/4/15, 7/2/15
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	PeRC Meeting: 2/24/16
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	2/12/16
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Mid-cycle Communication *(indicate date of mtg)*	☒ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	4/14/16
Cross-Discipline Team Leader Review *(indicate date for each review)*	4/14/16 and 4/12/16
PMR/PMC Development Templates *(indicate total number)*	2 PMRs

Clinical	
Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review co-signed review dated 4/5/16
• Clinical review(s) *(indicate date for each review)*	4/5/16, 8/11/15 (filing review)
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☒ and include a review/memo explaining why not *(indicate date of review/memo)*	See: Filing review dated 8/11/15, page 3 of 4
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*[5]	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review co-signed review dated 4/25/16
Statistical Team Leader Review(s) *(indicate date for each review)*	4/25/16
Statistical Review(s) *(indicate date for each review) asked for memo to file*	☒ None
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review Co-signed 3/18/16 review
Clinical Pharmacology review(s) *(indicate date for each review)*	3/18/16
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

[5] For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review co-signed 4/11/16 review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	4/11/16
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews[6]	
• Tertiary review (*indicate date for each review*)	☒ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	3/29/16
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	1/24/16: Method Validation Review
❖ Environmental Assessment (check one) (original and supplemental applications)	
☐ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	
☐ Review & FONSI *(indicate date of review)*	
☒ Review & Environmental Impact Statement *(indicate date of each review)*	See: Quality Assessment page 80 of 137
❖ Facilities Review/Inspection	
☐ Facilities inspections (*action must be taken prior to the re-evaluation date*) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable Re-evaluation date: ☐ Withhold recommendation ☐ Not applicable

[6] Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☐ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☐ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

Pediatric Research Equity Act (PREA) Waiver Request, Deferral Request/Pediatric Plan and Assessment Template(s)

BACKGROUND

Please check all that apply: ☐ **Full Waiver** ☐ **Partial Waiver** ☐ **Pediatric Assessment** ☒ **Deferral/Pediatric Plan**

BLA/NDA#: NDA 208551

PRODUCT PROPRIETARY NAME:
Triferic (Soluble Ferric Pyrophosphate)

ESTABLISHED/GENERIC NAME:

APPLICANT/SPONSOR:
Rockwell Medical, Inc.

PREVIOUSLY APPROVED INDICATION/S:
(1) _____
(2) _____
(3) _____
(4) _____

PROPOSED INDICATION/S:
*(1) _ Iron replacement product for the treatment of iron loss and maintenance of hemoglobin in adult patients with hemodialysis dependent chronic kidney disease*_____
(2) _____
(3) _____
(4) _____

BLA/NDA STAMP DATE: June 25, 2015

PDUFA GOAL DATE: April 25, 2016

SUPPLEMENT TYPE:

SUPPLEMENT NUMBER:

Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

NEW ☐ active ingredient(s) (includes new combination); ☐ indication(s); ☒ dosage form; ☐ dosing regimen; or ☐ route of administration?

Did the sponsor submit an Agreed iPSP? Yes ☒ No ☐

Did FDA confirm its agreement to the sponsor's Agreed iPSP? Yes ☒ No ☐

Has the sponsor submitted a Proposed Pediatric Study Request (PPSR) or does the Division believe there is an additional public health benefit to issuing a Written Request for this product, even if the plan is to grant a waiver for this indication? (Please note, Written Requests may include approved and unapproved indications and may apply to the entire moiety, not just this product.)

Yes ☐ No ☒

Is this application in response to a PREA (Postmarketing Requirement) PMR? Yes ☐ No ☒

If Yes, PMR # _____ NDA # _____

Does the division agree that this is a complete response to the PMR? Yes ☐ No ☐

If Yes, to either question Please complete the Pediatric Assessment Template.

If No, complete all appropriate portions of the template, including the assessment template if the division believes this application constitutes an assessment for any particular age group.

would be impossible or highly impractical.

- actinic keratosis
- adjunctive treatment of major depressive disorder
- age-related macular degeneration
- Alzheimer's disease
- amyloidosis
- amyotrophic lateral sclerosis
- androgenic alopecia
- atherosclerotic cardiovascular disease
- autosomal dominant polycystic kidney disease (ADPKD)
- benign monoclonal gammopathy
- benign prostatic hyperplasia
- cancer:
  - basal cell and squamous cell skin cancer
  - bladder
  - breast
  - cervical
  - colorectal
  - endometrial
  - esophageal
- cancer (continued):
  - follicular lymphoma
  - gastric
  - hairy cell leukemia
  - hepatocellular
  - indolent non-Hodgkin lymphoma
  - lung (small & non-small cell)
  - multiple myeloma
  - oropharynx (squamous cell)
  - ovarian (non-germ cell)
  - pancreatic
  - prostate
  - refractory advanced melanoma
  - renal cell
  - uterine
- chronic lymphocytic leukemia
- chronic obstructive pulmonary disease
- cryoglobulinemia
- diabetic peripheral neuropathy / macular edema
- digestive disorders (gallstones)

dry eye syndrome (keratoconjunctivitis sicca)

erectile dysfunction

essential thrombocytosis

Huntington's chorea

infertility & reproductive technology

ischemic vascular diseases, such as angina, myocardial infarction, and ischemic stroke

memory loss

menopause and perimenopausal disorders

mesothelioma

myelodysplasia

myelofibrosis & myeloproliferative disorders

osteoarthritis

overactive bladder

Parkinson's disease

paroxysmal nocturnal hemoglobinuria

plasma cells and antibody production disorders

polycythemia vera

postmenopausal osteoporosis

prevention of stroke and systemic embolic events in atrial fibrillation

psoriatic arthritis

reduction of thrombotic cardiovascular events in patients with coronary artery disease

replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone

retinal vein occlusions

stress urinary incontinence

temporary improvement in the appearance of caudal lines

treatment of incompetent great saphenous veins and varicosities

type 2 diabetic nephropathy

vascular dementia/vascular cognitive disorder/impairment

DEFERRAL REQUEST

Please attach:

☐ ***Pediatric Record***

1. **Age groups included in the deferral request: Birth to less than 18years of age**

2. **Where deferral is only requested for certain age groups, reason(s) for not including entire pediatric population in deferral request:**

3. **Reason/s for requesting deferral of pediatric studies in pediatric patients with disease:** (***Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for <u>each</u> age group or indication. This section should reflect the Division's thinking.***)

   a. **Adult studies are completed and ready for approval**
   b. Additional safety or effectiveness data needed (**describe**)
   c. Other (**specify**)

4. **Provide projected date for the submission of the pediatric assessment (deferral date): June 2021**

5. **Did applicant provide certification of grounds for deferring assessments?** ☒ **Yes** ☐ **No**

6. **Did applicant provide evidence that studies will be done with due diligence and at the earliest possible time?** ☒ **Yes** ☐ **No**

SPONSOR'S PROPOSED PEDIATRIC PLAN

1. **Has a pediatric plan been submitted to the Agency?** ☒ **Yes** ☐ **No**

2. Does the division agree with the sponsor's plan? ☒ **Yes** ☐ **No**

3. **Did the sponsor submit a timeline for the completion of must include at least dates for protocol submission, study completion and studies submitted)? ☒ Yes ☐ No**
    a. **Protocol Submission:**
    b. **Study Completion:**
    c. **Study Submission:**

Study 1:
Estimated protocol submission date: Not later than March 2015
Estimated study initiation date: Not later than September 2015
Estimated final report submission date: Not later than June 2017
Study 2:
Estimated protocol submission date: Not later than March 2018
Estimated study initiation date: Not later than September 2018
Estimated final report submission date: Not later than December 2020

4. **Has a Written Request been issued? ☐ Yes ☒ No (If yes and the WR matches the proposed pediatric plan, please attach a copy. It is not necessary to complete the remainder of this document)**

5. **Has a PPSR been submitted? ☐ Yes ☒ No (If yes, you may submit a draft WR and have PeRC review WR and deferral/plan at the same time.)**

Please note that the remainder of this section should be completed based on what the Division is requiring regardless of what the sponsor is proposing.

DIVISION'S PROPOSED PK, SAFTEY, AND EFFICACY TRIAL

Please complete as much of the information below as possible. Please note that the portions of the document that are shaded are not required for early stage pediatric plans but are useful if available.

Types of Studies/Study Design:
Study 1:
Title: Pharmacokinetics of FPC iron delivered via dialysate in pediatric patients with chronic kidney disease on hemodialysis.
Study Design: (b) (4)

Study 2:
Title: (b) (4)

(b) (4)

Study Design: (b) (4)

Nonclinical Studies:

Clinical Studies:

Age group and population (indication) in which study will be performed:
This section should list the age group and population exactly as it is in the plan.

(b) (4)

Example:
Study 1: patients aged X to Y years.
Study 2: sufficient number of subjects to adequately characterize the pharmacokinetics in the above age groups.

Number of patients to be studied or power of study to be achieved:

(b) (4)

Entry criteria:
This section should list pertinent inclusion/exclusion criteria.
Study 2:
Inclusion and Exclusion criteria:

(b) (4)

[redacted]

Example:
Entry criteria: Pediatric patients with disease x diagnosed with laboratory test of LFTs
Patients must have a negative pregnancy test if female..

Clinical endpoints:
Study 2:
Primary Endpoint:

(b) (4)

Safety parametersExample:
Study 1: Clinical outcome and safety will be the primary endpoints.

Study 2: The primary pharmacokinetic analysis of (drug name, concentration, form etc) DRUG should attempt to include all the patients in the study with determination of the following parameters: single dose and steady state AUC, Cmax, Tmax, and CL/F.

Timing of assessments:

Example :baseline, week 1, 4, and 6

Statistical information (statistical analyses of the data to be performed):
Example:
Study 1 non-inferiority: two-sided 95% confidence interval (CI) of treatment difference in improvement rates should be within 25% of the control's response rate.

Study 2: descriptive statistical methods for AUC, C max, Tmax, Cl/F and compared to adults.

Division comments on product safety:
Are there any safety concerns currently being assessed? ☐ **Yes** ☒ **No**

Are there safety concerns that require us to review post-marketing safety data before fully designing the pediatric studies? ☐ **Yes** ☒ **No**

Will a DSMB be required? ☐ **Yes** ☒ **No**

Other comments:

Division comments on product efficacy: Agreed with the proposed efficacy evaluation.

Division comments on sponsor proposal to satisfy PREA: Agreed with the proposal.

PeRC ASSESSMENT TEMPLATE

Please attach:

☐ ***Proposed Labeling from the sponsor unless the Division plans to change. If changing the language, include the appropriate language at the end of this form.***

☐ ***Pediatric Record***

Date of PREA PMR:

Description of PREA PMR: ***(Description from the PMC database is acceptable)***

Was Plan Reviewed by PeRC? ☐ **Yes** ☐ **No** If yes, did sponsor follow plan?

If studies were submitted in response to the Written Request (WR), provide the annotated WR in lieu of completing the remainder of the Pediatric Assessment template.

Indication(s) that were studied:
This section should list the indication(s) exactly as written in the *protocols.*

Example:
DRUG for the treatment of the signs and symptoms of disease x.

Number of Centers _____

Number and Names of Countries _____

Drug information:

Examples in italics

- **Route of administration**: *Oral*
- ***Formulation:** *disintegrating tablet*
- **Dosage:** *75 and 50 mg*
- **Regimen:** *list frequency of dosage administration*

**If the dosage form is powder for oral suspension; provide information on storage statement and concentration after reconstitution (e.g. with water, juice or apple sauce etc.)*

Types of Studies/ Study Design:
Example:
Study 1: Multi- center, randomized, active controlled double blind study to evaluate the safety and efficacy of (drug name, concentration, form etc) DRUG administered twice daily for the treatment of patients with disease x.
Study 2: PK and safety study of (drug name, concentration, form etc) DRUG in patients with disease x.

Age group and population in which study/ies was/were performed:

Example:
Study 1: patients aged X to Y years.
Study 2: sufficient number of patients to adequately characterize the pharmacokinetics in the above age groups.

Number of patients studied or power of study achieved:
Example:
Study 1: X patients in each treatment arm and was powered to show that (drug name, concentration, form etc) DRUG is not inferior to the active comparator. 50% were females and 25% were less than 3 years.

Study 2: powered and structured to detect a 30% change in (drug name, concentration, form etc) DRUG clearance and other relevant pharmacokinetic parameters. The study included at least X evaluable patients. .

Entry criteria:
This section should list pertinent inclusion/exclusion criteria.

Example:
Entry criteria: Pediatric patients with disease x diagnosed with laboratory test of LFTs
Patients had a negative pregnancy test if female.

Clinical endpoints:

Example:
Study 1: Clinical outcome and safety were the primary endpoints.

Study 2: The primary pharmacokinetic analysis of (drug name, concentration, form etc) DRUG attempted to include all the patients in the study with determination of the following parameters: single dose and steady state AUC, Cmax, Tmax, and CL/F

Statistical information (statistical analyses of the data performed): This section should list the statistical tests conducted. *Example:* *Study 1 - two-sided 95% confidence interval (CI) of treatment difference in improvement rates were within 25% of the control's response rate.* *Study 2: descriptive statistical methods for AUC, C max, Tmax, Cl/F and compared to adults.*
Timing of assessments: *Example:* *Baseline, week 2, week, 6, and end of treatment*
Division comments and conclusions (Summary of Safety and Efficacy)
Provide language Review Division is proposing for the appropriate sections of the label if different from sponsor-proposed language.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KIMBERLY L SCOTT
04/27/2016

Scott, Kimberly

From: Scott, Kimberly
Sent: Friday, April 08, 2016 4:20 PM
To: bdevarakonda@rockwellmed.com
Subject: NDA 208551 Triferic: USPI FDA Edits: DUE 10am, Monday, 4/11/16
Attachments: NDA 208551 Triferic USPI FDA Edits 4 8 2015 Tracked version wo.docx

Importance: High

Tracking:

Recipient	Read
bdevarakonda@rockwellmed.com	
Scott, Kimberly (Kimberly.Scott@fda.hhs.gov)	
Scott, Kimberly	Read: 4/8/2016 4:31 PM

Good afternoon Dr. Devarakonda,

Please refer to Triferic, NDA 208551 submitted June 25, 2015. Please find attached the FDA's proposed revision to Rockwell Medical's submission for Triferic (ferric pyrophosphate citrate) powder iron packet for the replacement of iron to maintain hemoglobin in adult patients with hemodialysis-dependent chronic kidney disease (HDD-CKD).

As discussed, the FDA has additional (attached) proposed edits with comments embedded within the USPI for NDA 208551 Triferic. Please review and provide revisions or comments to the attached FDA USPI. Using the same document, please remember to "save" your changes, and provide your comments in the following manner:

- Where you agree with the labeling revisions, "accept" the tracked changes.
- Where you disagree with the labeling revisions, provide your comments, and proposed language (shown in tracked changes). If necessary, edit the text but do not "reject" the FDA-proposed changes.

If you agree with the entire Agency's recommended revision, please send me an email stating you concur.

We request your response by **10:00AM (ET), Monday, April 11, 2016**.

Please acknowledge receipt of this email.

Thank you,
Kim
Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Rm 2222
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

10 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

KIMBERLY L SCOTT
04/22/2016

Scott, Kimberly

From: Scott, Kimberly
Sent: Friday, April 22, 2016 2:10 PM
To: bdevarakonda@rockwellmed.com
Subject: RE: NDA 208551 Triferic: Post Marketing Requirements:Agreement to be sent via gateway

Importance: High

Good afternoon Dr. Devarakonda,

Thank you for agreeing with the language and scheduled milestones in regards to the PREA PMR's for NDA 208551, Triferic. Please be sure to submit your formal response via the gateway.

Thank you,
Kim
Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Rm 2222
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

From: Bharathi Devarakonda [mailto:bdevarakonda@rockwellmed.com]
Sent: Friday, April 08, 2016 3:12 PM
To: Scott, Kimberly
Cc: Ray Pratt
Subject: RE: NDA 208551 Triferic: Post Marketing Requirements: request

Good Afternoon Cdr. Kim,

As requested, I am sending this email is to confirm that Rockwell concurs with the language and scheduled milestones of PREA Post Marketing Requirement (PMR). Please advise if the formal response should be submitted through the FDA gateway.

Sincerely,

Bharathi Devarakonda, Ph.D., RAC
Director, Regulatory Affairs

ROCKWELL MEDICAL
30142 Wixom Rd . Wixom MI 48393
Phone: 248-960-9009 (office); (b) (6) (Mobile)
Fax: 248-960-9119

Email: bdevarakonda@rockwellmed.com
www.rockwellmed.com

From: Scott, Kimberly [mailto:Kimberly.Scott@fda.hhs.gov]
Sent: Friday, April 08, 2016 12:46 PM
To: Bharathi Devarakonda <bdevarakonda@rockwellmed.com>
Cc: Ray Pratt <rpratt@rockwellmed.com>
Subject: RE: NDA 208551 Triferic: Post Marketing Requirements: request
Importance: High

Good afternoon Dr. Devarakonda,

As discussed, please review the following descriptions of both PREA Post Marketing Requirement (PMR) Descriptions and scheduled milestones:

1. PMR Description:

   Efficacy and safety trial of Triferic via hemodialysate in pediatric patients aged less than 18 years with hemodialysis-dependent chronic kidney disease.

   PMR Schedule Milestones: Final Protocol Submission: 03/31/2018
   Trial Completion: 07/31/2020
   Final Report Submission: 12/31/2020

2. PMR Description:

   Complete the trial and submit the final report for the pediatric pharmacokinetic trial entitled "Pharmacokinetics of SFP iron delivered via dialysate in pediatric patients with chronic kidney disease on hemodialysis."

   PMR Schedule Milestones: Final Protocol Submitted: 03/31/2015
   Trial Completion: 02/28/2017
   Final Report Submission: 06/30/2017

If agreed with the language and scheeduled milestone dates, please send an email stating you concur. The Agency will need your response by no later than 9:00am Monday, April 11, 2016

Thank you,
Kim

Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Rm 2222
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

From: Bharathi Devarakonda [mailto:bdevarakonda@rockwellmed.com]
Sent: Thursday, April 07, 2016 8:57 AM
To: Scott, Kimberly

Cc: Ray Pratt
Subject: RE: NDA 208551 Triferic: Post Marketing Requirements: request

Good Morning Cdr. Kim,

I am acknowledging the receipt of your email. Could you please send us the following additional details to proceed with responding to your email request.

For comment 1 - Attachments of labeling and PMR drafts as mentioned in your email.

For comment 2 - While we work on the PMR protocols and study reports, could you please clarify if there is anything that we are required to submit at this time and the timelines for submission.

Thank you,
Bharathi Devarakonda, Ph.D., RAC
Director, Regulatory Affairs

ROCKWELL MEDICAL
30142 Wixom Rd . Wixom MI 48393
Phone: 248-960-9009 (office); (b) (6) (Mobile)
Fax: 248-960-9119
Email: bdevarakonda@rockwellmed.com
www.rockwellmed.com

From: Scott, Kimberly [mailto:Kimberly.Scott@fda.hhs.gov]
Sent: Wednesday, April 06, 2016 8:05 PM
To: Bharathi Devarakonda <bdevarakonda@rockwellmed.com>
Cc: Ray Pratt <rpratt@rockwellmed.com>
Subject: NDA 208551 Triferic: Post Marketing Requirements: request
Importance: High

Good evening Dr. Devarakonda,

As we continue our review of your application, Triferic NDA 208551, our normal policy is to consider post-marketing studies at this time, so that they can be completed in advance of the action date. We have determined that the following clinical trials are necessary as post-marketing requirements (PMRs) based on the data available to date. We may have additional PMRs/PMCs later. These brief descriptions of the necessary studies/trials are intended to describe the main objective and trial characteristics of interest. Please provide edits and comments in clarifying mutually acceptable descriptions of the key trial elements. It is also necessary for you to provide schedule milestone dates as indicated. Most Milestones only require the applicant to provide the month and year for completion of each category (PREA Milestones require month, day, and year). For milestone calculation purposes only, assume that an approval occurs on the PDUFA date.

Upon mutual agreement, we ask you to submit both by email and officially a copy of the PMR's trial description to us with a statement that you agree to perform the trials as described and within the timelines that you specify for the trial.
Final PMR designation numbers will be assigned later.

Some things you can do to expedite this process:

1. For labeling and PMR's, reply to our drafts ASAP, and be sure to send me a courtesy copy by email. Reply with your edits in a WORD document that you submit by email as well as to the document room. Use track

changes to show YOUR edits. ACCEPT all of the track changes edits of ours with which you agree. You may provide annotation within the PI or, if extensive, in a separate document.

2. Assuming, and following a favorable action, you will then be submitting protocols intended to address the objectives of the PMRs agreed upon. We ask the following:

   a. For any new studies, it is necessary to submit the protocol for DHP review and concurrence prior to initiating. Note that the "Final Protocol Submission" date is the date by which you HAVE submitted a complete protocol and DHP has advised you that the protocol is judged acceptable to address the PMR. A fulfillment decision requires review.

   b. Send me an email courtesy copy of the draft versions, in WORD, as well as to the EDR officially. Again, for iterations, accept track changes sent to you that you agree with, and only return to us YOUR edits in track changes.

   c. It is critical that you advise, prominently, both with the email and cover letter to the EDR that the protocol you are sending is to address a SPECIFIC POST MARKETING REQUIREMENT (WITH THE PMR NUMBER). This helps the document room and us code the submission properly. All protocol submissions are made to the IND.

The Agency has the following Post Marketing Requirements for NDA 208551, Triferic Powder Packet:

PMR Description:	Efficacy and safety trial of Triferic via hemodialysate in pediatric patients chronic kidney disease.	
PMR Schedule Milestones:	ol Submission:	03/31/2018
	Trial Completion:	07/31/2020
	Final Report Submission:	12/31/2020

PMR Description:	Complete the trial and submit the final report for the pediatric pharmacokin *dialysate in pediatric patients with chronic kidney disease on hemodialysis."*	
PMR Schedule Milestones:		
	Final Protocol Submitted:	03/31
	Trial Completion:	02/28
	Final Report Submission:	06/30

Please acknowledge receipt of this email.

APPEARS THIS WAY ON ORIGINAL

Kind regards,
Kimberly

Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Rm 2222
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

THE INFORMATION CONTAINED IN THIS E-MAIL MESSAGE AND ANY ATTACHMENT IS CONFIDENTIAL INFORMATION INTENDED ONLY FOR THE INDIVIDUAL OR ENTITY NAMED ABOVE. This e-mail message and any attachments may contain communication which is privileged and confidential, and the disclosure of this information outside of the intended recipient is strictly prohibited and governed by applicable law. If the reader of this e-mail message is not the intended recipient, or the employee or agent respons ble to deliver it to the intended recipient, you are hereby notified that any review, distribution, or copying of this communication is strictly prohibited. If you have received this communication in error, please immediately notify the sender by return e-mail or by calling (248) 960-9009, and delete this e-mail message and any attachments from your computer. Thank you.

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/s/

KIMBERLY L SCOTT
04/22/2016

Scott, Kimberly

From: Scott, Kimberly
Sent: Wednesday, April 06, 2016 7:47 PM
To: bdevarakonda@rockwellmed.com
Cc: Ray Pratt
Subject: NDA 208551 Triferic: Post Marketing Requirements: request

Importance: High

Good evening Dr. Devarakonda,

As we continue our review of your application, Triferic NDA 208551, our normal policy is to consider post-marketing studies at this time, so that they can be completed in advance of the action date. We have determined that the following clinical trials are necessary as post-marketing requirements (PMRs) based on the data available to date. We may have additional PMRs/PMCs later. These brief descriptions of the necessary studies/trials are intended to describe the main objective and trial characteristics of interest. Please provide edits and comments in clarifying mutually acceptable descriptions of the key trial elements. It is also necessary for you to provide schedule milestone dates as indicated. Most Milestones only require the applicant to provide the month and year for completion of each category (PREA Milestones require month, day, and year). For milestone calculation purposes only, assume that an approval occurs on the PDUFA date.

Upon mutual agreement, we ask you to submit both by email and officially a copy of the PMR's trial description to us with a statement that you agree to perform the trials as described and within the timelines that you specify for the trial.
Final PMR designation numbers will be assigned later.

Some things you can do to expedite this process:

1. For labeling and PMR's, reply to our drafts ASAP, and be sure to send me a courtesy copy by email. Reply with your edits in a WORD document that you submit by email as well as to the document room. Use track changes to show YOUR edits. ACCEPT all of the track changes edits of ours with which you agree. You may provide annotation within the PI or, if extensive, in a separate document.

2. Assuming, and following a favorable action, you will then be submitting protocols intended to address the objectives of the PMRs agreed upon. We ask the following:

    a. For any new studies, it is necessary to submit the protocol for DHP review and concurrence prior to initiating. Note that the "Final Protocol Submission" date is the date by which you HAVE submitted a complete protocol and DHP has advised you that the protocol is judged acceptable to address the PMR. A fulfillment decision requires review.

    b. Send me an email courtesy copy of the draft versions, in WORD, as well as to the EDR officially. Again, for iterations, accept track changes sent to you that you agree with, and only return to us YOUR edits in track changes.

    c. It is critical that you advise, prominently, both with the email and cover letter to the EDR that the protocol you are sending is to address a SPECIFIC POST MARKETING REQUIREMENT (WITH THE PMR NUMBER). This helps the document room and us code the submission properly. All protocol submissions are made to the IND.

The Agency has the following Post Marketing Commitment's for NDA 208551, Triferic Powder Packet:

PMR Description:	Efficacy and safety trial of Triferic via hemodialysate in pediatric patients chronic kidney disease.	
PMR Schedule Milestones:	ol Submission:	03/31/2018
	Trial Completion:	07/31/2020
	Final Report Submission:	12/31/2020

PMR Description:	Complete the trial and submit the final report for the pediatric pharmacokin *dialysate in pediatric patients with chronic kidney disease on hemodialysis."*	
PMR Schedule Milestones:		
	Final Protocol Submitted:	03/31
	Trial Completion:	02/28
	Final Report Submission:	06/30

Please acknowledge receipt of this email.

APPEARS THIS WAY ON ORIGINAL

Kind regards,
Kimberly

Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Rm 2222
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

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/s/

KIMBERLY L SCOTT
04/06/2016

Scott, Kimberly

From: Scott, Kimberly
Sent: Wednesday, April 06, 2016 8:11 PM
To: bdevarakonda@rockwellmed.com
Cc: Ray Pratt
Subject: RE: NDA 208551 Triferic: Post Marketing Requirements: request

Importance: High

Good evening Dr. Devarakonda,

Please note the correction in red text below. The Agency has the following Post Marketing "Requirements," not Commitments.

Thank you,
Kim

From: Scott, Kimberly
Sent: Wednesday, April 06, 2016 8:05 PM
To: bdevarakonda@rockwellmed.com
Cc: 'Ray Pratt'
Subject: NDA 208551 Triferic: Post Marketing Requirements: request
Importance: High

Good evening Dr. Devarakonda,

As we continue our review of your application, Triferic NDA 208551, our normal policy is to consider post-marketing studies at this time, so that they can be completed in advance of the action date. We have determined that the following clinical trials are necessary as post-marketing requirements (PMRs) based on the data available to date. We may have additional PMRs/PMCs later. These brief descriptions of the necessary studies/trials are intended to describe the main objective and trial characteristics of interest. Please provide edits and comments in clarifying mutually acceptable descriptions of the key trial elements. It is also necessary for you to provide schedule milestone dates as indicated. Most Milestones only require the applicant to provide the month and year for completion of each category (PREA Milestones require month, day, and year). For milestone calculation purposes only, assume that an approval occurs on the PDUFA date.

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Final PMR designation numbers will be assigned later.

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2. Assuming, and following a favorable action, you will then be submitting protocols intended to address the objectives of the PMRs agreed upon. We ask the following:

a. For any new studies, it is necessary to submit the protocol for DHP review and concurrence prior to initiating. Note that the "Final Protocol Submission" date is the date by which you HAVE submitted a complete protocol and DHP has advised you that the protocol is judged acceptable to address the PMR. A fulfillment decision requires review.

b. Send me an email courtesy copy of the draft versions, in WORD, as well as to the EDR officially. Again, for iterations, accept track changes sent to you that you agree with, and only return to us YOUR edits in track changes.

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	Trial Completion:	07/31/2020
	Final Report Submission:	12/31/2020

PMR Description:	Complete the trial and submit the final report for the pediatric pharmacokin *dialysate in pediatric patients with chronic kidney disease on hemodialysis."*	
PMR Schedule Milestones:		
	Final Protocol Submitted:	03/31
	Trial Completion:	02/28
	Final Report Submission:	06/30

Please acknowledge receipt of this email.

APPEARS THIS WAY ON ORIGINAL

Kind regards,
Kimberly

Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Rm 2222
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

APPEARS THIS WAY ON ORIGINAL

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/s/

KIMBERLY L SCOTT
04/06/2016

Laiq, Rabiya

From:	Laiq, Rabiya
Sent:	Friday, March 25, 2016 2:10 PM
To:	'Bharathi Devarakonda'
Cc:	Baird, Amy
Subject:	FDA Information Request NDA 208551- Please Respond by March 28, 2016.
Importance:	High

Dear Bharathi:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Triferic (Ferric Pyrophosphate Citrate).

We also refer to your June 25, 2015 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Process Deficiency

1. ***There are two contradicting Master Batch Records for packaging – one in section 3.2.P.3.3 (submitted in the original application and one in section 3.2.P.3.1 (the one updated after Information Request #1). Please remove the original MBR and move the updated one to section 3.2.P.3.3.***

If you have any questions, please contact me, at (240) 402-6153. Please respond by **March 28, 2016**.

Please submit an email copy of the response followed by a formal submsion through the FDA gateway.

Kindly confirm receipt of this email.

Thanks,
Rabiya

Scott, Kimberly

From: Scott, Kimberly
Sent: Thursday, March 24, 2016 4:07 PM
To: 'Bharathi Devarakonda'
Cc: Ray Pratt; Carrie Guss
Subject: RE: NDA 208551 Triferic : USPI and Carton Container Label:

Good afternoon Dr. Devarakonda,

Although the Agency would like for the NDC number on the 5 mL ampule label, the NDC number is not required per 21 CFR 201.2. Additionally, 21 CFR 201.10(i) has allowances for small labels and as such the NDC number is not required. Therefore, we agree with your request not to display the NDC number on the 5 mL ampule label, as long as it is displayed on the pouch and carton labeling as they indicated.

Please acknowledge receipt of this email.

Thank you,
Kim
Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Rm 2222
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

From: Bharathi Devarakonda [mailto:bdevarakonda@rockwellmed.com]
Sent: Thursday, March 24, 2016 3:37 PM
To: Scott, Kimberly
Cc: Ray Pratt; Carrie Guss
Subject: RE: NDA 208551 Triferic : USPI and Carton Container Label: DUE 1PM, Wednesday, 3/16

Good Afternoon Kim,

Per our discussion on Monday, you intended to get back to us yesterday with an answer on whether we can consider the Package insert final based on the prior approval of the 5 mL ampule without an NDC number. I am just following up to see if you have received an answer yet. Please let me know so we may proceed with our printing.

Thank you,
Bharathi Devarakonda, Ph.D., RAC
Director, Regulatory Affairs

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Fax: 248-960-9119
Email: bdevarakonda@rockwellmed.com

www.rockwellmed.com

From: Scott, Kimberly [mailto:Kimberly.Scott@fda.hhs.gov]
Sent: Monday, March 21, 2016 2:26 PM
To: Bharathi Devarakonda <bdevarakonda@rockwellmed.com>
Cc: Ray Pratt <rpratt@rockwellmed.com>
Subject: RE: NDA 208551 Triferic : USPI and Carton Container Label: DUE 1PM, Wednesday, 3/16

Good afternoon Dr. Devarakonda,

This is to acknowledge receipt of your response. I will forward your comments to the review team.

Thank you,
Kim

Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Rm 2222
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

From: Bharathi Devarakonda [mailto:bdevarakonda@rockwellmed.com]
Sent: Monday, March 21, 2016 2:25 PM
To: Scott, Kimberly
Cc: Ray Pratt
Subject: RE: NDA 208551 Triferic : USPI and Carton Container Label: DUE 1PM, Wednesday, 3/16

Good Afternoon Cdr Kim,

Reference is made to the Labeling Amendment submitted to the Agency on March 16, 2016 as Seq0013, where all the recommendations as proposed by the agency were accepted, except for the requested NDC number for the 5 mL ampule container.

Reference is also made to the telephone conversation on March 21, 2016 between Cdr Kimberly Scott, and the Rockwell Team: Dr. Bharathi Devarakonda, Director of Regulatory Affairs; Dr. Raymond Pratt, CMO; and Ms. Carrie Guss, Sr. Director of Clinical Research and Operations, regarding the agreement reached between Rockwell Medical and the agency at the time of approval, regarding the justification for not including the NDC number on the individual 5 mL ampule.

Per our conversation, we are providing the Final Approved Labeling for Triferic Solution, 5 mL ampule presentation, as approved on January 23, 2015 (see the attached). As previously discussed with the agency, the ampule size does not allow room for including the NDC number on the 5 mL ampule. At the time of labeling review and approval, it was agreed upon by the agency, that assignment of NDC codes for the pouch and carton labels of Triferic Solution, 5 mL ampule, would be sufficient, since the ampules are stored in the pouch until use. There have been no other changes to the 5 mL label since approval.

Given the prior approval of the 5 mL ampule label, we request that the Agency consider our justification, and provide approval of the Triferic package insert, so that we may proceed with printing in preparation for our commercial launch.

Please be advised that the electronic submission through the FDA gateway will be submitted tomorrow, March 22, 2016.

Thank you,

Bharathi Devarakonda, Ph.D., RAC
Director, Regulatory Affairs

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KIMBERLY L SCOTT
03/24/2016

PeRC Meeting Minutes
February 24, 2016

PeRC Members Attending:
Lynne Yao
Ikram Elayan
Kevin Krudys
Gettie Audain
Daiva Shetty
Meshaun Payne
Gerri Baer
Wiley Chambers
Julia Pinto
Maura O'Leary Non Responsive
Lili Mulugeta
Peter Starke
Ruthanna Davi
Raquel Tapia
Greg Reaman
Dionna Green
Barbara Buch
Rachel Witten
Michelle Roth-Kline
George Greeley

Agenda

Non Responsive

11:45	NDA 208551	Triferic (ferric pyrophosphate citrate) Deferral Plan	DHP	Kimberly Scott	The replacement of iron to maintain hemoglobin in adult patients with hemodialysis-dependent chronic kidney disease (HDD-CKD).

Non Responsive

4 Page(s) has been Withheld in Full as NON-RESPONSIVE immediately following this page

Non Responsive

Triferic (ferric pyrophosphate citrate) Deferral Plan (with an Agreed iPSP)

- Proposed Indication: The replacement of iron to maintain hemoglobin in adult patients with hemodialysis-dependent chronic kidney disease (HDD-CKD).
- PDUFA goal date is April 25, 2016.
- This application triggers PREA because the product is a new dosage form.
- The division was not available to review this pediatric plan. However, the pediatric plan is based on an Agreed iPSP and the division has no changes to the pediatric plan. The sponsor agreed to conduct studies in all pediatric age groups and is not requesting a waiver for any pediatric age groups.

- *PeRC Recommendations:*
    - The PeRC agreed with the Division's pediatric plan, including the granting of a deferral in all pediatric age groups because the adult studies are completed and ready for approval.
    - The PeRC requested confirmation from the division that the protocol for the PK study as outlined in the agreed iPSP was submitted in March, 2015.
- *Post PeRC comment:*
    - The division confirmed that the Pediatric PK Protocol was submitted by the sponsor.

Non Responsive

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GETTIE AUDAIN
03/18/2016

Scott, Kimberly

From: Scott, Kimberly
Sent: Thursday, March 10, 2016 1:40 PM
To: bdevarakonda@rockwellmed.com
Subject: NDA 208551 Triferic : USPI and Carton Container Label: DUE 1PM, Wednesday, 3/16
Attachments: NDA 208551 Triferic revised-draft-labeling-text-redline-word-3 10 16 .docx; draft-packet-label.pdf; draft-packet-label-callouts.pdf; draft-carton-label.pdf; draft-carton-label-callouts.pdf

Importance: High

Good afternoon Dr. Devarakonda,

Please refer to Triferic, NDA 208551 submitted June 25, 2015. Please find attached the FDA's proposed revision to Rockwell Medical's submission for Triferic (ferric pyrophosphate citrate) powder iron packet for the replacement of iron to maintain hemoglobin in adult patients with hemodialysis-dependent chronic kidney disease (HDD-CKD).

The FDA has attached the proposed edits with comments embedded within the USPI for NDA 208551 Triferic. Please review and provide revisions or comments to the attached FDA USPI. Using the same document, please remember to "save" your changes, and provide your comments in the following manner:

- Where you agree with the labeling revisions, "accept" the tracked changes.
- Where you disagree with the labeling revisions, provide your comments, and proposed language (shown in tracked changes). If necessary, edit the text but do not "reject" the FDA-proposed changes.

As discussed in previous correspondences (January 21 and 22, 2016), the Agency confirms the prominence of your established name for the carton/container label is acceptable, and have no further comments or changes to the Carton/Container Label.

We request your response by **1:00PM (ET), Wednesday, March 16, 2016**.

Please acknowledge receipt of this email.

Thank you,
Kim
Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
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Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

13 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KIMBERLY L SCOTT
03/10/2016

Laiq, Rabiya

From: Laiq, Rabiya
Sent: Wednesday, March 09, 2016 4:54 PM
To: 'Bharathi Devarakonda'
Cc: Baird, Amy
Subject: FDA Information Request NDA 208551- Please Respond by March 14, 2016.

Importance: High

Dear Bharathi:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Triferic (Ferric Pyrophosphate Citrate).

We also refer to your June 25, 2015 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. *Revise the shipping and storage conditions, and shipping label, for Drug Substance in the bulk shipping container from* (b) (4) (b) (4)

If you have any questions, please contact me, at (240) 402-6153. Please respond by **March 14, 2016.**

Please submit an email copy of the response followed by a formal submsion through the FDA gateway.

Kindly confirm receipt of this email.

Thanks,
Rabiya

DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=PIV, serialNumber=D72A10D821086D99CF8125A16859010C2B5A843C872A8243EE
Date: 2016.03.09 16:56:34 -05'00'

Scott, Kimberly

From: Scott, Kimberly
Sent: Tuesday, February 09, 2016 10:20 PM
To: 'Bharathi Devarakonda'
Cc: Ray Pratt
Subject: RE: NDA 208551 Triferic: Labeling Recommendations: Agency response

Good evening Dr. Devarakonda,

The Agency is working hard to review all the labeling documents (Prescribing Information, Carton/container labeling) and we hope to have additional FDA comments on the PI soon, but per the filing letter, the FDA timeline to send labeling comments is March 28, 2016. Also, if there are any additional FDA changes to the C/C labeling, we will forward as soon as we have it.

Please acknowledge receipt of this email.

Kind Regards,
Kim
Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Rm 2222
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

From: Bharathi Devarakonda [mailto:bdevarakonda@rockwellmed.com]
Sent: Monday, February 01, 2016 10:55 AM
To: Scott, Kimberly
Cc: Ray Pratt
Subject: RE: NDA 208551 Triferic: Labeling Recommendations: Agency response

Good Morning Ms. Kim,

Could you please update us on the feedback from the review team on our proposed labeling for Triferic Powder Packet, NDA 208551.

I appreciate your help.

Sincerely,
Bharathi Devarakonda, Ph.D., RAC
Director, Regulatory Affairs

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Phone: 248-960-9009 (office); (b) (6) (Mobile)
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Email: bdevarakonda@rockwellmed.com
www.rockwellmed.com

From: Bharathi Devarakonda
Sent: Monday, January 25, 2016 10:52 AM
To: 'Scott, Kimberly' <Kimberly.Scott@fda.hhs.gov>; Ray Pratt <rpratt@rockwellmed.com>
Subject: RE: NDA 208551 Triferic: Labeling Recommendations: Agency response

Good Morning Ms. Kim,

Thank you for acknowledging my email. We look forward to a quick feedback from the review team.

Sincerely,
Bharathi Devarakonda, Ph.D., RAC
Director, Regulatory Affairs

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Fax: 248-960-9119
Email: bdevarakonda@rockwellmed.com
www.rockwellmed.com

From: Scott, Kimberly [mailto:Kimberly.Scott@fda.hhs.gov]
Sent: Monday, January 25, 2016 10:49 AM
To: Bharathi Devarakonda <bdevarakonda@rockwellmed.com>; Ray Pratt <rpratt@rockwellmed.com>
Subject: RE: NDA 208551 Triferic: Labeling Recommendations: Agency response

Good morning Dr. Devarakonda,

I am acknowledging receipt of your email, and will discuss your request with our team.

Regards,
Kim
Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Rm 2222
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

From: Bharathi Devarakonda [mailto:bdevarakonda@rockwellmed.com]
Sent: Friday, January 22, 2016 9:45 PM
To: Scott, Kimberly; Ray Pratt
Subject: RE: NDA 208551 Triferic: Labeling Recommendations: Agency response

Good evening Ms. Kim,

I am acknowledging receipt of your email. As mentioned in our earlier email communications, the User Fee Goal Date for the NDA 208551 is April 25, 2016. The lead time for availability of (b) (4) components and labels are approximately (b) (4) and we are preparing for commercial launch of the product immediately upon receiving approval of the NDA. Therefore, to facilitate a timely launch once we receive approval, we request the Agency to kindly review and provide additional comments on the labeling or confirmation that the labeling is acceptable by January 29 2015.

Thank you and the review team for your assistance with this request.

Sincerely,
Bharathi Devarakonda, Ph.D., RAC
Director, Regulatory Affairs

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From: Scott, Kimberly [mailto:Kimberly.Scott@fda.hhs.gov]
Sent: Friday, January 22, 2016 5:15 PM
To: Bharathi Devarakonda <bdevarakonda@rockwellmed.com>; Ray Pratt <rpratt@rockwellmed.com>
Subject: RE: NDA 208551 Triferic: Labeling Recommendations: Agency response

Good evening Dr. Devarakonda,

The Agency is still reviewing the Triferic labeling, and there will be additional comments on the PI. We can only confirm that the prominence of your established name for the carton/container label is acceptable. Therefore, they might be other comments on the carton/container labels.

Please acknowledge receipt of this email.

Thank you,
Kim
Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Rm 2222
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

From: Bharathi Devarakonda [mailto:bdevarakonda@rockwellmed.com]
Sent: Friday, January 22, 2016 3:49 PM
To: Scott, Kimberly; Ray Pratt
Subject: RE: NDA 208551 Triferic: Labeling Recommendations: Agency response

Good afternoon Ms. Kim,

Just so we are clear, labeling is acceptable we mean the package insert, container and carton labels. Please confirm there will be no additional comments coming for package insert of NDA 208551.

Sincerely,
Bharathi Devarakonda, Ph.D., RAC
Director, Regulatory Affairs

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www.rockwellmed.com

From: Bharathi Devarakonda
Sent: Thursday, January 21, 2016 6:38 PM
To: Scott, Kimberly <Kimberly.Scott@fda.hhs.gov>; Ray Pratt <rpratt@rockwellmed.com>
Subject: Re: NDA 208551 Triferic: Labeling Recommendations: Agency response

Good Evening Ms. Kim,

Thank you for confirming us that the current proposed labeling for NDA 208551, Triferic Powder Packet, is acceptable. We will be proceeding with printing of labeling for commercial use.

Please advise if the Agency will be sending us a withdrawal letter of Labeling Recommendations received via an email on January 20, 2016.

Thank you once again for facilitating communications with the review team very promptly.

Sincerely,
Bharathi
Sent from my iPhone

On Jan 21, 2016, at 3:55 PM, "Scott, Kimberly" <Kimberly.Scott@fda.hhs.gov> wrote:

> Good afternoon Dr. Devarakonda,
>
> The Agency has considered your concerns regarding our labeling recommendations for NDA 208551, Triferic. Your rationale appears reasonable; therefore, we accept their request to maintain the current proposed labeling. A teleconference will not be necessary.
>
> Please acknowledge receipt of this email.
>
> Kind Regards,
> Kim
> **Kimberly Scott, RN, BSN, OCN®**
> CDR, U.S. Public Health Service
> Regulatory Health Project Manager
> Division of Hematology Products
> Office of Hematology and Oncology Products
> Center for Drug Evaluation and Research
> Food and Drug Administration
> 10903 New Hampshire Avenue, Bldg. 22, Rm 2222

Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

From: Bharathi Devarakonda [mailto:bdevarakonda@rockwellmed.com]
Sent: Thursday, January 21, 2016 8:57 AM
To: Scott, Kimberly
Cc: Ray Pratt
Subject: RE: NDA 208551 Triferic: Labeling Recommendations Due January 25, 2016

Good Morning Ms. Kim,

Please see our question below for which we could like to receive further clarifications from the Agency.

- For creating labeling for Triferic powder packet, we used the file with same proprietary and established names as well as the logo that is currently being approved for marketed 5 mL and 50 mL presentations of Triferic Solution. Therefore, we believe that the proposed label for Triferic Powder packet is in accordance with 21CFR 210.10(g)(2).

We are available any time today and tomorrow for a teleconference with the review team. Call in numbers are as provided below:

US Dial In: 877-366-0711
Leader Code: 95604754
Participant Code: 18470718

Thank you,
Bharathi Devarakonda, Ph.D., RAC
Director, Regulatory Affairs

<image001.jpg>
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Email: bdevarakonda@rockwellmed.com
www.rockwellmed.com

From: Scott, Kimberly [mailto:Kimberly.Scott@fda.hhs.gov]
Sent: Wednesday, January 20, 2016 9:52 PM
To: Bharathi Devarakonda <bdevarakonda@rockwellmed.com>
Cc: Ray Pratt <rpratt@rockwellmed.com>
Subject: RE: NDA 208551 Triferic: Labeling Recommendations Due January 25, 2016

Good evening,

Thank you for your response. I will let the team know you will be sending your question tomorrow.

Regards,
Kimberly
Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service

Regulatory Health Project Manager
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Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
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Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

From: Bharathi Devarakonda [mailto:bdevarakonda@rockwellmed.com]
Sent: Wednesday, January 20, 2016 8:27 PM
To: Scott, Kimberly
Cc: Ray Pratt
Subject: Re: NDA 208551 Triferic: Labeling Recommendations Due January 25, 2016

Good Evening Ms. Kim,

I acknowledge the receipt of your email.

For creating labeling for Triferic powder packet, we used the file with same proprietary and established names as well as the logo that is currently being approved for marketed 5 mL and 50 mL presentations of Triferic Solution. Therefore, we believe that the proposed label for Triferic Powder packet is in accordance with 21CFR 210.10(g)(2).

However, I will discuss with my team and send you the list of questions before noon tomorrow.

Thank you and have a wonderful evening!

Sincerely,
Bharathi

Sent from my iPhone

On Jan 20, 2016, at 7:04 PM, "Scott, Kimberly" <Kimberly.Scott@fda.hhs.gov> wrote:

> Good evening Dr. Devarakonda,
>
> Please send the list of questions you would like to discuss in regards to clarification on the comments sent related to the labeling for Triferic Powder Packet on 20 January 2016.
>
> Please confirm receipt of this email.
>
> Thank you,
> Kim
> **Kimberly Scott, RN, BSN, OCN®**
> CDR, U.S. Public Health Service
> Regulatory Health Project Manager
> Division of Hematology Products
> Office of Hematology and Oncology Products
> Center for Drug Evaluation and Research

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Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

From: Scott, Kimberly
Sent: Wednesday, January 20, 2016 6:01 PM
To: 'Bharathi Devarakonda'
Cc: Ray Pratt
Subject: RE: NDA 208551 Triferic: Labeling Recommendations Due January 25, 2016

Good evening Dr. Devarakonda,

I am acknowledging receipt of your email, and apologize for the late response. I will discuss with the reviewers regarding a teleconference with you and your team.

Thank you,
Kim
Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Rm 2222
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

From: Bharathi Devarakonda [mailto:bdevarakonda@rockwellmed.com]
Sent: Wednesday, January 20, 2016 11:27 AM
To: Scott, Kimberly
Cc: Ray Pratt
Subject: FW: NDA 208551 Triferic: Labeling Recommendations Due January 25, 2016

Good Morning Ms. Kimberly,

I would like to reach out to you requesting some clarifications on the labeling comments received for Triferic Powder Packet on 20 January 2016.

Please be advised that the printing features of the established name i.e. typography, layout, and contrast with respect to the proprietary name of Triferic Powder Packet are exactly the same as that currently used for approved labeling for Triferic Solution, 5 mL and 50 mL ampule, which are in accordance with 21 CFR 201.10(g)(2). The file used for the names and the logo is the same one we used for the labeling for the 5 and 50 mL marketed presentation. Please see the attached approved labels for 50 mL ampule for your reference. We would like to schedule a brief telephone call with yourself and the reviewer responsible for the powder packet to reach an agreement on this issue today.

Sincerely,
Bharathi Devarakonda, Ph.D., RAC
Director, Regulatory Affairs

<image001.jpg>

30142 Wixom Rd . Wixom MI 48393
Phone: 248-960-9009 (office); (b) (6) (Mobile)
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Email: bdevarakonda@rockwellmed.com
www.rockwellmed.com

From: Bharathi Devarakonda
Sent: Wednesday, January 20, 2016 11:26 AM
To: Scott, Kimberly <Kimberly.Scott@fda.hhs.gov>
Cc: Bharathi Devarakonda <bdevarakonda@rockwellmed.com>; Ray Pratt <rpratt@rockwellmed.com>
Subject: RE: NDA 208551 Triferic: Labeling Recommendations Due January 25, 2016

Good Morning Ms. Kimberly,

I would like to reach out to you requesting some clarifications on the labeling comments received for Triferic Powder Packet on 20 January 2016.

Please be advised that the printing features of the established name i.e. typography, layout, and contrast with respect to the proprietary name of Triferic Powder Packet are exactly the same as that currently used for approved labeling for Triferic Solution, 5 mL and 50 mL ampule, which are in accordance with 21 CFR 201.10(g)(2). The file used for the names and the logo is the same one we used for the labeling for the 5 and 50 mL marketed presentation. Please see the attached approved labels for 50 mL ampule for your reference. We would like to schedule a brief telephone call with yourself and the reviewer responsible for the powder packet to reach an agreement on this issue today.

Sincerely,
Bharathi Devarakonda, Ph.D., RAC
Director, Regulatory Affairs

<image001.jpg>
30142 Wixom Rd . Wixom MI 48393
Phone: 248-960-9009 (office); (b) (6) (Mobile)
Fax: 248-960-9119
Email: bdevarakonda@rockwellmed.com
www.rockwellmed.com

From: Scott, Kimberly [mailto:Kimberly.Scott@fda.hhs.gov]
Sent: Wednesday, January 20, 2016 8:16 AM
To: Bharathi Devarakonda <bdevarakonda@rockwellmed.com>
Cc: Scott, Kimberly <Kimberly.Scott@fda.hhs.gov>
Subject: NDA 208551 Triferic: Labeling Recommendations Due January 25, 2016
Importance: High

Good morning Dr. Devarakonda,

The Agency has recommendations for Rockwell Medical Inc. regarding NDA 208551, Triferic. We recommend the following be implemented prior to approval of NDA 208551:
:

A. Triferic Carton Labeling

a. The established name lacks prominence commensurate with the proprietary name. Increase the prominence of the established name taking into
account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).

B. Triferic Container (Packet) Label
a. See recommendation A.a. and revise accordingly.

Please respond to the Agency in regards to the recommended changes for the carton container label by 10:00am (ET) Monday, January 25, 2016.

Please acknowledge receipt of this email.

Thank you,
Kim
Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
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Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

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/s/

KIMBERLY L SCOTT
02/09/2016

Scott, Kimberly

From: Scott, Kimberly
Sent: Thursday, January 21, 2016 3:56 PM
To: bdevarakonda@rockwellmed.com
Subject: RE: NDA 208551 Triferic: Labeling Recommendations: Agency response

Importance: High

Good afternoon Dr. Devarakonda,

The Agency has considered your concerns regarding our labeling recommendations for NDA 208551, Triferic. Your rationale appears reasonable; therefore, we accept their request to maintain the current proposed labeling. A teleconference will not be necessary.

Please acknowledge receipt of this email.

Kind Regards,
Kim
Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Rm 2222
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

From: Bharathi Devarakonda [mailto:bdevarakonda@rockwellmed.com]
Sent: Thursday, January 21, 2016 8:57 AM
To: Scott, Kimberly
Cc: Ray Pratt
Subject: RE: NDA 208551 Triferic: Labeling Recommendations Due January 25, 2016

Good Morning Ms. Kim,

Please see our question below for which we could like to receive further clarifications from the Agency.

- For creating labeling for Triferic powder packet, we used the file with same proprietary and established names as well as the logo that is currently being approved for marketed 5 mL and 50 mL presentations of Triferic Solution. Therefore, we believe that the proposed label for Triferic Powder packet is in accordance with 21CFR 210.10(g)(2).

We are available any time today and tomorrow for a teleconference with the review team. Call in numbers are as provided below:

US Dial In: 877-366-0711
Leader Code: 95604754
Participant Code: 18470718

Thank you,
Bharathi Devarakonda, Ph.D., RAC
Director, Regulatory Affairs

ROCKWELL MEDICAL
30142 Wixom Rd . Wixom MI 48393
Phone: 248-960-9009 (office); (b) (6) (Mobile)
Fax: 248-960-9119
Email: bdevarakonda@rockwellmed.com
www.rockwellmed.com

From: Scott, Kimberly [mailto:Kimberly.Scott@fda.hhs.gov]
Sent: Wednesday, January 20, 2016 9:52 PM
To: Bharathi Devarakonda <bdevarakonda@rockwellmed.com>
Cc: Ray Pratt <rpratt@rockwellmed.com>
Subject: RE: NDA 208551 Triferic: Labeling Recommendations Due January 25, 2016

Good evening,

Thank you for your response. I will let the team know you will be sending your question tomorrow.

Regards,
Kimberly
Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Rm 2222
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

From: Bharathi Devarakonda [mailto:bdevarakonda@rockwellmed.com]
Sent: Wednesday, January 20, 2016 8:27 PM
To: Scott, Kimberly
Cc: Ray Pratt
Subject: Re: NDA 208551 Triferic: Labeling Recommendations Due January 25, 2016

Good Evening Ms. Kim,

I acknowledge the receipt of your email.

For creating labeling for Triferic powder packet, we used the file with same proprietary and established names as well as the logo that is currently being approved for marketed 5 mL and 50 mL presentations of Triferic Solution. Therefore, we believe that the proposed label for Triferic Powder packet is in accordance with 21CFR 210.10(g)(2).

However, I will discuss with my team and send you the list of questions before noon tomorrow.

Thank you and have a wonderful evening!

Sincerely,
Bharathi

Sent from my iPhone

On Jan 20, 2016, at 7:04 PM, "Scott, Kimberly" <Kimberly.Scott@fda.hhs.gov> wrote:

> Good evening Dr. Devarakonda,
>
> Please send the list of questions you would like to discuss in regards to clarification on the comments sent related to the labeling for Triferic Powder Packet on 20 January 2016.
>
> Please confirm receipt of this email.
>
> Thank you,
> Kim
> **Kimberly Scott, RN, BSN, OCN®**
> CDR, U.S. Public Health Service
> Regulatory Health Project Manager
> Division of Hematology Products
> Office of Hematology and Oncology Products
> Center for Drug Evaluation and Research
> Food and Drug Administration
> 10903 New Hampshire Avenue, Bldg. 22, Rm 2222
> Silver Spring, MD 20993
> Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov
>
> ---
>
> **From:** Scott, Kimberly
> **Sent:** Wednesday, January 20, 2016 6:01 PM
> **To:** 'Bharathi Devarakonda'
> **Cc:** Ray Pratt
> **Subject:** RE: NDA 208551 Triferic: Labeling Recommendations Due January 25, 2016
>
> Good evening Dr. Devarakonda,
>
> I am acknowledging receipt of your email, and apologize for the late response. I will discuss with the reviewers regarding a teleconference with you and your team.
>
> Thank you,
> Kim
> **Kimberly Scott, RN, BSN, OCN®**
> CDR, U.S. Public Health Service
> Regulatory Health Project Manager
> Division of Hematology Products
> Office of Hematology and Oncology Products
> Center for Drug Evaluation and Research
> Food and Drug Administration
> 10903 New Hampshire Avenue, Bldg. 22, Rm 2222

Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

From: Bharathi Devarakonda [mailto:bdevarakonda@rockwellmed.com]
Sent: Wednesday, January 20, 2016 11:27 AM
To: Scott, Kimberly
Cc: Ray Pratt
Subject: FW: NDA 208551 Triferic: Labeling Recommendations Due January 25, 2016

Good Morning Ms. Kimberly,

I would like to reach out to you requesting some clarifications on the labeling comments received for Triferic Powder Packet on 20 January 2016.

Please be advised that the printing features of the established name i.e. typography, layout, and contrast with respect to the proprietary name of Triferic Powder Packet are exactly the same as that currently used for approved labeling for Triferic Solution, 5 mL and 50 mL ampule, which are in accordance with 21 CFR 201.10(g)(2). The file used for the names and the logo is the same one we used for the labeling for the 5 and 50 mL marketed presentation. Please see the attached approved labels for 50 mL ampule for your reference. We would like to schedule a brief telephone call with yourself and the reviewer responsible for the powder packet to reach an agreement on this issue today.

Sincerely,
Bharathi Devarakonda, Ph.D., RAC
Director, Regulatory Affairs

<image001.jpg>
30142 Wixom Rd . Wixom MI 48393
Phone: 248-960-9009 (office); (b) (6) (Mobile)
Fax: 248-960-9119
Email: bdevarakonda@rockwellmed.com
www.rockwellmed.com

From: Bharathi Devarakonda
Sent: Wednesday, January 20, 2016 11:26 AM
To: Scott, Kimberly <Kimberly.Scott@fda.hhs.gov>
Cc: Bharathi Devarakonda <bdevarakonda@rockwellmed.com>; Ray Pratt <rpratt@rockwellmed.com>
Subject: RE: NDA 208551 Triferic: Labeling Recommendations Due January 25, 2016

Good Morning Ms. Kimberly,

I would like to reach out to you requesting some clarifications on the labeling comments received for Triferic Powder Packet on 20 January 2016.

Please be advised that the printing features of the established name i.e. typography, layout, and contrast with respect to the proprietary name of Triferic Powder Packet are exactly the same as that currently used for approved labeling for Triferic Solution, 5 mL and 50 mL ampule, which are in accordance with 21 CFR 201.10(g)(2). The file used for the names and the logo is the same one we used for the labeling for the 5 and 50 mL marketed presentation. Please see the attached approved labels for 50 mL ampule for your reference. We would like to schedule a brief telephone call with yourself and the reviewer responsible for the powder packet to reach an agreement on this issue today.

Sincerely,

Bharathi Devarakonda, Ph.D., RAC
Director, Regulatory Affairs

<image001.jpg>
30142 Wixom Rd . Wixom MI 48393
Phone: 248-960-9009 (office); (b) (6) (Mobile)
Fax: 248-960-9119
Email: bdevarakonda@rockwellmed.com
www.rockwellmed.com

From: Scott, Kimberly [mailto:Kimberly.Scott@fda.hhs.gov]
Sent: Wednesday, January 20, 2016 8:16 AM
To: Bharathi Devarakonda <bdevarakonda@rockwellmed.com>
Cc: Scott, Kimberly <Kimberly.Scott@fda.hhs.gov>
Subject: NDA 208551 Triferic: Labeling Recommendations Due January 25, 2016
Importance: High

Good morning Dr. Devarakonda,

The Agency has recommendations for Rockwell Medical Inc. regarding NDA 208551, Triferic. We recommend the following be implemented prior to approval of NDA 208551:
:

A. Triferic Carton Labeling
   a. The established name lacks prominence commensurate with the proprietary name. Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).

B. Triferic Container (Packet) Label
   a. See recommendation A.a. and revise accordingly.

Please respond to the Agency in regards to the recommended changes for the carton container label by 10:00am (ET) Monday, January 25, 2016.

Please acknowledge receipt of this email.

Thank you,
Kim
Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Rm 2222
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

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/s/

KIMBERLY L SCOTT
01/21/2016

Scott, Kimberly

From: Scott, Kimberly
Sent: Wednesday, January 20, 2016 8:16 AM
To: 'Bharathi Devarakonda'
Cc: Scott, Kimberly
Subject: NDA 208551 Triferic: Labeling Recommendations Due January 25, 2016

Importance: High

Good morning Dr. Devarakonda,

The Agency has recommendations for Rockwell Medical Inc. regarding NDA 208551, Triferic. We recommend the following be implemented prior to approval of NDA 208551:
:

A. Triferic Carton Labeling

a. The established name lacks prominence commensurate with the proprietary name. Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).

B. Triferic Container (Packet) Label

a. See recommendation A.a. and revise accordingly.

Please respond to the Agency in regards to the recommended changes for the carton container label by 10:00am (ET) Monday, January 25, 2016.

Please acknowledge receipt of this email.

Thank you,
Kim
Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Rm 2222
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

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/s/

KIMBERLY L SCOTT
01/20/2016

Scott, Kimberly

From: Scott, Kimberly
Sent: Monday, December 28, 2015 11:41 AM
To: 'bdevarakonda@rockwellmed.com'
Subject: NDA 208551 Triferic: Labeling Recommendations DUE 1/6/16

Importance: High

Tracking:

Recipient	Read	Recall
'bdevarakonda@rockwellmed.com'		
Scott, Kimberly	Deleted: 12/28/2015 11:50 AM	Succeeded: 12/28/2015 11:50 AM

Good morning Dr. Devarakonda,

The Agency has recommendations for Rockwell Medical Inc. for NDA 208551 Triferic Label. We recommend the following be implemented prior to approval of NDA 208551:

A. Health Care Provider Education

a. To decrease the risk of medication errors caused by confusion between current and proposed Triferic formulations, we recommend that Rockwell Medical consider providing education to HCPs regarding the availability of different dosage forms of Triferic. The education may be provided through Dear Health Care Provider Letter, dialysis nurse education, and in-service presentations.

B. Triferic Carton Labeling

a. The established name lacks prominence commensurate with the proprietary name. Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).

b. Revise the statement [redacted] (b) (4) to "Must be diluted in 25 gallons of bicarbonate concentrate prior to use." This revision will add prominence to the dilution volume and may help to mitigate the risk of medication errors due to incorrect dilution.

c. The container label of one packet and the carton labeling of 100 packets should have different NDC numbers. Revise the NDC numbers so that the carton labeling and packet label NDC numbers are different for these two package configurations.

d. Remove the statement [redacted] (b) (4) We recommend this revision due to post-marketing reports that negative statements (e.g., do not) may have the opposite of the intended meaning because the word [redacted] (b) (4) can be overlooked and misinterpret the warning as an affirmative action.1

e. Consider relocating the sponsor information ("Rockwell Medical") to the side panel(s) as it clutters the PDP and takes readers' attention away from important prescribing information, such as proprietary name and strength.

C. Triferic packet label

a. See recommendations in Sections A.a. through A.e. and revise packet label accordingly.

Please respond to the Agency in regards to the recommended changes for the label by 10:00am (ET) Wednesday, January 6, 2016.

Please acknowledge receipt of this email.

Thank you,
Kim
Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Rm 2222
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

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/s/

KIMBERLY L SCOTT
12/29/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208551

INFORMATION REQUEST

Rockwell Medical Inc.
Attention: Raymond D Pratt, MD, FACP
Chief Medical Officer
30142 S. Wixom Road
Wixom, MI 48393

Dear Dr. Pratt:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Triferic (Ferric Pyrophosphate Citrate).

We also refer to your June 25, 2015 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Regulatory

1. Explain how the changes proposed in NDA 206317 supplemental applications 03 (alternate drug substance batch size and manufacturing process (b) (4) as an alternate testing site), and (b) (4) as an alternate site for drug substance manufacture and control) are to be incorporated into NDA 208551.

Drug Substance

2. Update the following sections in NDA 208551to reflect the information approved in NDA 206317:
    a. NDA section 3.2.S.1 for the molecular weight, formula and structure and USAN name.
    b. NDA section 3.2.S.2 for the complete and current manufacturing information.
    c. NDA section 3.2.S.3.2 for the acceptance specifications for starting materials.

3. Revise the release specification in NDA section 3.2.S.4.1 to use the approved specification in NDA 206317:

a. include the test for [redacted] assay (with a criterion of [redacted]%);
b. include identification testing for sulfate and citrate;
c. report the test result for residual [redacted] as "ppm" (instead of [redacted] and
d. report the test result for BET as "EU/mg".

4. Regarding description of method MI 1127:
   a. Specify the typical or acceptable ranges for constants a0 and a1 in the calculation.
   b. Specify the detection limit for each metal determined by this method.
   c. Update the method validation study to address [redacted] for solution stability and method variation.
   d. Provide batch history and analysis data for lot 1305397 used in the method validation study.

5. Revise NDA section 3.2.S.2.1 to specify the tests to be performed [redacted] Also, either provide complete validation studies for each test performed at each site or reference the documents in NDA 206317 that provide the method validation study.

6. Provide lot history information and lot release testing data for [redacted] drug substance lots 1305364, 1305412-A and 1405441 that were used to manufacture the drug product registration batches. Also, provide any available stability study data on these lots.

7. For the [redacted] drug substance lots used to manufacture the drug product registration batches, provide the test results for residual [redacted]

8. In NDA section 3.2.S.6, provide a description, acceptance specification and example supplier certificate of analysis for the [redacted]

9. Regarding the submitted stability study data:
   a. Provide any additional study data on lot 1004939; NDA 206317 indicated that the study on this lot was on-going.
   b. Provide any additional stability study data which supports the currently proposed [redacted] month retest period in the current packaging system.

10. Provide comparative measurements of the level [redacted] drug substance.

Drug Product

11. Regarding the release specification in NDA 3.2.P.5.1:
    a. Specify when sampling for release testing is performed.
    b. Establish and justify acceptance criteria [redacted] and net weight; and specify whether these values are determined on finished product samples or on samples obtained during product manufacture.

c. Revise the anion assay criteria for sulfate, phosphate and pyrophosphate [redacted]
d. Establish an acceptance criterion for total iron [redacted]
e. Establish an acceptance criterion for net weight. Also, describe the difference between the in-process control for fill weight and the release specification for net weight

12. The stability specification for "Bacterial Endotoxin Test" provided in NDA section 3.2.P.8 Stability Report [redacted] SP-14-007-R is [redacted] EU/mg. Furthermore, the data for the stability batches do not match the release specification of [redacted] EU/mg established in NDA section 3.2.P.5.1 for "Bacterial Endotoxins". Explain this inconsistency and update relevant sections of the submission with the correct specification.

13. Revise NDA section 3.2.P.3.1 to specify the identity and assay tests to be performed at [redacted] Also, either provide a complete validation study for each test at each site or reference the documents in NDA 206317 which provides the method validation study.

14. Update the submitted batch analysis data to provide the following data and information:
    a. the results for identification of sulfate and citrate;
    b. the results for [redacted] assay.
    c. the results for total iron [redacted]
    d. a copy of the [redacted] certificate of conformance for each NDA registration batch.

15. Establish an acceptance specification for the packaging [redacted] This should include testing for identity and thickness of each [redacted] and inspection of the supplier certificate of analysis. Also, provide a copy of a typical supplier certificate of analysis or conformation.

16. Regarding the submitted stability information:
    a. Specify the facility that performed each test in the study.
    b. NDA section 3.2.P.8.1 indicates that the registration studies at 30°C are on-going, however Stability Report SP-14-007-R in NDA section 3.2.P.8.3 indicates that the registration studies at 30°C are complete. Please clarify.
    c. Provide the results from the 18 month sample for the NDA registration studies at 25°C and 30°C. Also, provide test results from the registration studies at [redacted] C.
    d. For the post approval stability commitments, verify that the registration batch studies will continue through [redacted] and that annual batches thereafter will follow the described protocol.
    e. For future stability studies, [redacted]

1 Page has been Withheld in Full as b4 (CCI/TS) immediately following this page

If you have any questions, please contact me, at (240) 402-6153. Please respond by December 3, 2015.

Sincerely,

Rabiya Laiq -A

Digitally signed by Rabiya Laiq -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Rabiya Laiq -A, 0.9.2342.19200300.100.1.1=2001555007
Date: 2015.11.19 14:10:00 -05'00'

Rabiya Laiq, Pharm.D.
Regulatory Business Process Manager
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208551

METHODS VALIDATION MATERIALS RECEIVED

Rockwell Medical Inc.
Attention: Dr. Raymond Pratt, MD
30142 S. Wixom Road
Wixom, MI 48393
Telephone: 248 960 9009
Email: rpratt@rockwellmed.com

Dear Dr. Pratt:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Triferic (ferric pyrophosphate citrate powder for solution, 272 mg iron (III)) and to our 9/10/2015, letter requesting sample materials for methods validation testing.

We acknowledge receipt on 9/29/2015, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3811), FAX (314-539-2113), or email (Michael.Hadwiger@fda.hhs.gov).

Sincerely,

Michael E. Hadwiger, Ph.D.
MVP Coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

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/s/

MICHAEL E HADWIGER
10/02/2015
NDA 208551 material request acknowledgement

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208551

REQUEST FOR METHODS VALIDATION MATERIALS

Rockwell Medical Inc.
Attention: Dr. Raymond Pratt, MD
30142 S. Wixom Road
Wixom, MI 48393
Telephone: 248 960 9009
Email: rpratt@rockwellmed.com

Dear Dr. Pratt:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Triferic (ferric pyrophosphate citrate powder for solution, 272 mg iron (III)).

We will be performing methods validation studies on Triferic (ferric pyrophosphate citrate powder for solution, 272 mg iron (III)), as described in NDA 208551.

In order to perform the necessary testing, we request the following sample materials and equipment:

Method, current version

Method(s)	Method #
Identification - Ferric Iron by ICP-OES Assay - Fe by Inductively Coupled Plasma - Optical Emission Spectroscopy	505094001 - ICPOES
Identification - Pyrophosphate by Ion Chromatography Assay - Sulfate, Phosphate, Citrate, Pyrophosphate by Ion Chromatography	505094001 - SO4C1, PO4C1, P2O7C1, CITC1
Assay - Sodium by Ion Chromatography	505094001 - NaCl

Samples and Reference Standards

Reagent	Minimum Mass or Volume Required	Units
	(b) (4)	mg
		mg
		mg
		mg
		mg
Fe ICP/DCP Standard Solution	(b) (4)	mL
Triferic (ferric pyrophosphate citrate powder for solution, 272 mg iron (III)) drug substance	(b) (4)	mg

Equipment

(b) (4)

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: MVP Sample Custodian
645 S Newstead
St. Louis, MO 63110

Please notify me upon receipt of this FAX. You may contact me by telephone (314-539-3811), FAX (314-539-2113), or email (michael.hadwiger@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael E. Hadwiger, Ph.D.
MVP coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

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/s/

MICHAEL E HADWIGER
09/10/2015
materials request for NDA 208551

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208551

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

Rockwell Medical Inc.
Attention: Bharathi Devarakonda, PhD, RAC
Director, Regulatory Affairs
30142 S. Wixom Road
Wixom, MI 48393

Dear Dr. Devarakonda:

Please refer to your New Drug Application (NDA) dated June 25, 2015, received June 25, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Triferic® (ferric pyrophosphate citrate) Powder, 272 mg iron (III)/packet.

We also refer to your amendments dated July 6, 14, 15, and 31, 2015.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is April 25, 2016.

We are reviewing your application according to the processes described in the Guidance for Review *Staff and Industry: Good* Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by March 28, 2016.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments or questions:

1. Highlights (HL) Indication and Usage Heading: The established pharmacologic class (EPC) is not listed following the product name under the Indications and Usage heading. The concise statement under this heading in HL must identify the EPC as follows: (Drug) is a (EPC) indicated for (indication(s)). The EPC for Triferic is iron replacement product.

2. Table of Content Section

    a. Subsections 8.2, 8.3, and 8.4 headings need to be renumbered as follows:
        8.3 Nursing Mothers
        8.4 Pediatric Use
        8.5 Geriatric Use

    b. Subsection 12.2 Pharmacokinetics heading needs to be renumbered as
        12.3 Pharmacokinetics.

3. Full Prescribing Information Section

    a. Subsection 8.2, 8.3, and 8.4 headings need to be renumbered as follows:
        8.3 Nursing Mothers
        8.4 Pediatric Use
        8.5 Geriatric Use

    b. Section 11 Description in the June 25, 2015 submission, original proposed labeling, describes Triferic powder. However, Section 11 Description in the July 15, 2015, latest amended draft labeling, describes Triferic solution product. Please revise Section 11 to describe the powder to support this application proposed powder dosage form.

c. Subsection 12.2 Pharmacokinetics needs to be renumbered as 12.3 Pharmacokinetics.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by September 14, 2015. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the

product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full deferral request is denied.

If you have any questions, call Jacquin Jones, Regulatory Project Manager, at (240) 402-4590.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AMY C BAIRD
09/04/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208551

NDA ACKNOWLEDGMENT

Rockwell Medical Inc.
Attention: Raymond D. Pratt, MD, FACP
Chief Medical Officer
30143 S. Wixom Road
Wixom, MI 48393

Dear Dr. Pratt:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Triferic (ferric pyrophosphate citrate) powder, 272 mg iron(III)/packet

Date of Application: June 25, 2015

Date of Receipt: June 25, 2015

Our Reference Number: NDA 208551

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 24, 2015, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at http://www.fda.gov/opacom/morechoices/fdaforms/default.html.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at: http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm. Additional information regarding Title VIII of FDAAA is available at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html. Additional information for registering your clinical trials is available at the Protocol Registration System website http://prsinfo.clinicaltrials.gov/.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **NDA 208551** submitted on June 25, 2015, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient

information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, please call me at (240) 402-4590.

Sincerely,

{See appended electronic signature page}

Jacquin L. Jones, BSN, MS
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JACQUIN L JONES
07/02/2015