

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212320Orig1s000

OTHER REVIEW(S)

CLINICAL INSPECTION SUMMARY

Date	May 22, 2019
From	Min Lu, M.D., M.P.H., Medical Officer Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Laurel Menapace, M.D., Medical Officer Tanya Wroblewski, M.D., Clinical Team Leader Rachel McMullen, M.P.H., M.H.A., Regulatory Project Manager Division of Division of Hematology Products (DHP)
NDA	NDA 212320
Applicant	Shield Therapeutics (UK) Ltd.
Drug	Ferric Maltol
NME	No
Therapeutic Classification	Oral iron product
Proposed Indication	Treatment of iron deficiency anemia in subjects with chronic kidney disease
Consultation Request Date	November 9, 2018
Summary Goal Date	August 27, 2019
Action Goal Date	September 27, 2019
PDUFA Date	September 27, 2019

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two clinical sites (Drs. Block and Kharait) were selected for inspection for a Phase 3 study (Protocol ST10-01-303), entitled “A phase 3, randomized, placebo controlled, prospective, multicenter study with oral ferric maltol for the treatment of iron deficiency anemia in subjects with chronic kidney disease.” The study data derived from these clinical sites, based on the inspections and as submitted by the sponsor, are considered reliable in support of this application.

The final regulatory compliance classification of Dr. Block’s site is No Action Indicated (NAI). The preliminary regulatory compliance classification of Dr. Kharait’s site is Voluntary Action Indicated (VAI). Although protocol violations/deviations were noted, they appear unlikely to have significant impact on the primary efficacy endpoint of the study. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

2. BACKGROUND

Ferric maltol is an oral iron product. The sponsor submitted a 505(b)(2) application for ferric maltol for the proposed indication for the treatment of iron deficiency anemia (IDA) in patients with chronic kidney disease (CKD) not on dialysis. The sponsor conducted a Phase 3 study (Protocol ST10-303) to support the proposed indication. An interim study report was submitted after the end of the double-blind treatment period of the study. The study is currently ongoing for the open-label treatment period to evaluate the safety.

Study ST10-303

Protocol Title: A phase 3, randomized, placebo controlled, prospective, multicenter study with oral ferric maltol for the treatment of iron deficiency anemia in subjects with chronic kidney disease.

Study ST10-303 is a multi-center, randomized (2:1 ratio), placebo-controlled study to compare oral ferric maltol 30 mg capsule twice daily to matching placebo for 16 weeks, followed by an open-label safety extension with ferric maltol treatment for 36 weeks in subjects with chronic kidney disease not on dialysis with iron deficiency anemia.

The primary objective of this study is to evaluate the efficacy of oral ferric maltol compared with placebo in the treatment of IDA in subjects with CKD at 16 weeks. The secondary objective of this study is to evaluate the efficacy, safety, tolerability and pharmacokinetics of ferric maltol in subject with IDA and CKD over a treatment duration of up to 52 weeks.

The primary efficacy endpoint is the change in hemoglobin (Hb) from baseline to Week 16. The secondary endpoints include the proportion of subjects that achieve an increase in Hb concentration of ≥ 1 g/dL at Week 16, the proportion of subjects that achieve a Hb concentration of ≥ 11 g/dL at Week 16, change in Hb concentration from baseline to Week 8, the proportion of subjects that achieve an increase in Hb concentration of ≥ 2 g/dL at Week 16, change in Hb concentration from baseline to Week 4, and changes in iron parameters (ferritin, transferrin saturation [TSAT], and serum iron).

The study inclusion criteria include adult patients with a current diagnosis of CKD with an estimated glomerular filtration rate (eGFR) of < 60 ml/min/1.73m² and ≥ 15 ml/min/1.73m²; iron deficiency anemia defined by the following criteria assessed via screening laboratory results: a. Hb < 11.0 g/dL and ≥ 8.0 g/dL, b. ferritin < 250 ng/mL with a TSAT $< 25\%$ OR ferritin < 500 ng/mL with a TSAT of $< 15\%$. Subjects with use of any following treatments prior to randomization are to be excluded from the study: IV iron injection within the previous 4 weeks or administration of intramuscular or depot iron preparation within the previous 12 weeks; oral iron supplementation, taken specifically to treat anemia (e.g., ferrous sulfate, fumarate, and gluconate) within the previous 2 weeks; use of ferric citrate and sucroferric oxyhydroxide within the previous 1 week; ESAs within the previous 4 weeks; blood transfusion or donation within the previous 12 weeks; dimercaprol or cloramphenicol within the previous 7 days; or current use of methyldopa. The above medications are also not permitted during the study.

The study consists of a screening period up to 14 days, a double-blind treatment period of 16 weeks with oral ferric maltol 30 mg capsule twice a day or oral matching placebo, an open-label treatment with ferric maltol for 36 weeks, and a post-treatment follow-up for 14 days.

The study screened 363 subjects and randomized 167 subjects from 30 sites in the United States. The study enrolled the first subjects on December 1, 2016. The study is ongoing. The interim study report was submitted with cut-off date of January 18, 2018 when the last subject completed the double-blind treatment period.

Rationale for Site Selection

Two clinical sites were selected based on the highest number of protocol violations in which patients who met withdrawal criteria were not appropriately withdrawn from study.

3. RESULTS (by site):

Clinical Investigator Sites for inspection	Protocol #/ Site #/ # of Subjects	Inspection Date	Classification
Dr. Geoffrey Block Denver Nephrologists, P.C. 130 Rampart Way, Suite 175 Denver, CO 80230	Protocol ST10-01-303 Site #101 Randomized subjects: 7	January 14-17, 2019	NAI
Dr. Sourabh Kharait 151 North Sunrise Avenue, Suite 1205 Roseville, CA 95661	Protocol ST10-01-303 Site #110 Randomized subjects: 7	January 28-31, 2019	VAI*

Key to Compliance Classifications

NAI (No Action Indicated) = No deviation from regulations.

VAI (Voluntary Action Indicated) = Deviation(s) from regulations.

OAI (Official Action Indicated) = Significant deviations from regulations. Data unreliable.

*Pending = Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

Clinical Study Site Investigators

1. Geoffrey Block, M.D. (Site# 101, Dever, CO)

The site screened eight subjects and enrolled seven subjects for Protocol ST10-01-303. Among the seven enrolled subjects, five subjects completed the double-blind treatment period of the study and two subjects in the ferric maltol group discontinued (one due to death [Subject (b) (6)] and another due to blood transfusion [Subject (b) (6)]). An audit was conducted for all eight subjects.

The inspection evaluated the following documents: source records, screening and enrollment logs, the study protocols and amendments, eligibility criteria, case report forms, laboratory results (hematology, chemistry and iron markers), physical examinations, electrocardiogram results, pharmacokinetics results, estimated Glomerular Filtration Rate (eGFR) results, progress notes, concomitant medication log, study drug accountability logs, study monitoring visits, efficacy endpoints, adverse event reporting, and correspondence. Informed consent documents, financial disclosure statement, IRB correspondence, and sponsor-generated correspondence were also inspected. Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. There were no limitations during conduct of the clinical site inspection.

Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events was noted. Protocol deviations were documented and reported to the sponsor.

The following issue was discussed at the end of inspection at the site:

- Information pertaining to withdrawal of the subjects due to serious adverse events/interventions was not transcribed into the electronic data capture (EDC) system within 3 business days of the corresponding study visit as per the eCRF Completion Guidelines V2.0 manual.

Specifically,

- During the double-blind treatment period, one subject [Subject (b) (6) in the ferric maltol group) had an early termination visit on (b) (6) due to blood transfusions received in hospital and the subject was not withdrawn from the study in the EDC system until (b) (6).
- During open-label ferric maltol treatment extension period, one subject (Subject (b) (6)) received two blood transfusions, the site became aware on (b) (6) and subject was not withdrawn from the study in the EDC system until (b) (6); another subject (Subject (b) (6)) had an early termination visit due to needed renal replacement therapy on (b) (6) and the subject was not withdrawn from the study in the EDC system until (b) (6).

OSI reviewer comment:

For Subject (b) (6) (ferric maltol group), the hemoglobin level on (b) (6) at the time of withdrawal due to blood transfusions was used as Week 16 hemoglobin level for the efficacy analysis. For Subjects (b) (6) (ferric maltol group) and (b) (6) (placebo group), withdrawal due to blood transfusions or renal replacement occurred after double-blind treatment period. Although protocol deviations are noted as described above, they appear unlikely to have significantly impact on the primary efficacy endpoint that was based on hemoglobin value at Week 16 at the end of double-blind treatment period.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued. Data submitted by this clinical site appear acceptable in support of this specific indication.

2. Sourabh Kharait, M.D. (Site# 110, Roseville, CA)

The site screened 10 subjects and enrolled six subjects for Protocol ST10-01-303. All enrolled six subjects completed the study. An audit was conducted for all ten screened subjects.

The inspection evaluated the following documents: source records, screening and enrollment logs, the study protocols and amendments, eligibility criteria, blinding/randomization, case report forms, study drug accountability logs, study monitoring visits, efficacy endpoints, adverse event reporting, and correspondence. Informed consent documents, financial disclosure statement, IRB correspondence, and sponsor-generated correspondence were also inspected. Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. There were no limitations during conduct of the clinical site inspection.

Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events was noted. Protocol deviations were documented and reported to the sponsor.

The following item was noted during the inspection:

- One subject (Subject (b) (6) in the ferric maltol group) who experienced two serious adverse events (fall with multiple rib fractures and pneumonia) received Venofer and Epogen on (b) (6), two prohibited concomitant medications in the protocol, which should lead to discontinuation from the study. However, investigator allowed the subject to continue the study.

OSI reviewer comment:

Subject (b) (6) was randomized to the ferric maltol group and received the first treatment dose on (b) (6) and the hemoglobin level on (b) (6) (prior to use prohibited medications) was used as Week 16 (should be on (b) (6)) hemoglobin level for the efficacy analysis. Although protocol violation is noted as described above, this appear unlikely to have significantly impact on the primary efficacy endpoint of the study.

In general, this clinical site appeared to be in compliance with Good Clinical Practices except the protocol violation noted above. A Form FDA 483 (Inspectional Observations) was not issued. Data submitted by this clinical site appear acceptable in support of this application.

{See appended electronic signature page}

Min Lu, M.D., M.P.H.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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Branch Chief
Good Clinical Practice Assessment Branch
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cc:

Central Doc. Rm.
Review Division / Acting Clinical Team Leader/ Tanya Wroblewski
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OSI/ GCP Program Analyst/Yolanda Patague

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/s/

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: May 17, 2019
Requesting Office or Division: Division of Hematology Products (DHP)
Application Type and Number: NDA 212320
Product Name and Strength: Accrufer (ferric maltol) capsules 30 mg
Applicant/Sponsor Name: Shield Therapeutics
FDA Received Date: May 8, 2019
OSE RCM #: 2018-2097-2
DMEPA Safety Evaluator: Stephanie DeGraw, PharmD
DMEPA Team Leader: Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Hematology Products requested we review the revised container label and carton labeling for Accrufer (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review^a and label and labeling review memo.^b

2 CONCLUSION

The revised container labeling is acceptable from a medication error perspective. We have no additional recommendations at this time.

^a DeGraw, S. Label and Labeling Review for Accrufer (ferric maltol) NDA 212320. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 MAR 4. RCM No.: 2018-2097.

^b DeGraw, S. Label and Labeling Review for Accrufer (ferric maltol) NDA 212320. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 APR 23. RCM No.: 2018-2097-1.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON MAY 8, 2019

Container Label



Carton Labeling



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/s/

STEPHANIE L DEGRAW
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Division of Hematology Products (DHP) Labeling Review

NDANumber	NDA 212320
Applicant	SHIELD TX UK LTD
Proprietary Name (nonproprietary name)	Accrufer (ferric maltol)
Receipt Date	09/27/2018
PDUFA Goal Date (Internal Goal Date)	07/27/19
Review Classification	Standard
Proposed Indication (or current indication if unchanged)	Accrufer is an iron replacement product indicated for the treatment of iron deficiency
Dosing Regimen	30 mg twice daily
From	Virginia Kwitkowski, MS, ACNP-BC Associate Director for Labeling, DHP

Background of Application:

In this review, I summarize the DHP labeling recommendations and edits in the Accrufer (ferric maltol) labeling. These edits are made to ensure that the prescribing information is a useful communication tool for healthcare providers and uses clear, concise language; is based on regulations and guidances; and conveys the essential scientific information needed for the safe and effective use of Accrufer (ferric maltol).

Upon receipt, I reviewed the proposed USPI and identified deficiencies throughout the labeling.

On 12/10/2018, FDA issued the Day 74 filing letter which included my initial labeling recommendations listed below.

Labeling Recommendations:

1. To avoid cluttering the label, we recommend inclusion of Trademark symbols only once in labeling; in the product title. Remove the trademark from everywhere except the product title.

2. Correct the cross-reference formatting: The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier of the Subsection. The entire cross-reference should be in *italics* (to achieve emphasis) and enclosed within brackets. The word “see” should be lower case. For example, [*see Use in Specific Populations (8.1)*].
3. Revise the Product Title in the Highlights Section: Refer to the Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products—Content and Format Guidance available at <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm592850.pdf>. “for oral use” is preferred.
4. Revise the indication (both in Highlights and the FPI) to be consistent with the Indications and Usage Guidance, which states that “age groups should be included in indications. As such, an indication should state that a drug is approved, for example, “in adults”, “in pediatric patients X years of age and older”, or “in adults and pediatric patients X years of age and older”.
5. Revise the Dosage Forms and Strength section of Highlights to reflect use of a heading that describes the dosage form. For example: “Capsules: 30mg”. Highlights should not include identifying characteristics of the dosage forms; these details would be provided in the Full Prescribing Information (FPI).
6. Remove the box from the 2nd Warning in Highlights and in FPI Warning 5.2. If your intention was to include a Boxed Warning, the Boxed Warning would be located just beneath the Initial U.S. Approval. However, other oral iron products do not contain a boxed warning for this risk.
7. Revise the Warnings & Precautions in Highlights to provide a Heading that is consistent with the headings in the FPI.
8. For the Use in Specific Populations:
The information in FPI 8.1 Pregnancy and 8.2 Lactation do not support inclusion of a pregnancy section in Highlights. Remove these two items from Highlights.
9. Revise the Drug Interactions section of Highlights to provide headings consistent with the FPI section.
10. Revise the FPI Dosage and Administrations Section to the following numbered subsections.
 - a. 2.1 Recommended Dosage (combine current contents of 2.1-2.3)
 - b. 2.2 Recommended Monitoring (add a subsection that describes any monitoring tests recommended before, during, and after therapy).
11. Revise the FPI Dosage Forms and Strengths to include a heading (the dosage form “Capsules”. Include the information you proposed, but add any identifying characteristics printed on the capsule.
12. Revise the FPI Contraindications section per the Warnings and Precautions Guidance which states that “along with the contraindication statement, the labeling should briefly describe the type and nature of the observed (or anticipated) reaction and a cross-reference to a more detailed discussion elsewhere in labeling..” Do not revise the Warning for Iron Overload as that text is required by regulation.
13. Revise the FPI Warnings to be consistent with the Warnings and Precautions guidance which states that each warning should contain a succinct description of the adverse reaction (AR) and

outcome; numerical estimate or AR rate; known risk factors for the AR; and steps to take to prevent, mitigate, monitor for, or manage the AR. We encourage you to refer to other approved labelings for similar products. Venofer could be considered a good example of Warnings content and format.

14. We recommend that you not include [REDACTED] (b) (4)
15. In the FPI Section 6 Adverse Reactions: Remove the [REDACTED] (b) (4) as it is not clinically meaningful.
16. Delete [REDACTED] (b) (4) (FPI) as there is no data.
17. FPI Section 7; Delete [REDACTED] (b) (4)
18. FPI Section 8.4: Replace the existing statement with the required verbatim statement per 201.57(c)(9)(iv)(F): "Safety and effectiveness have not been established in pediatric patients."
19. FPI Section 8.5: Revise this section per the regulations. Per 21CFR 201.57, specific statements on geriatric use of the drug for an indication approved for adults generally, as distinguished from a specific geriatric indication, must be contained in the "Geriatric use" subsection and must reflect all information available to the sponsor that is relevant to the appropriate use of the drug in elderly patients.
20. Delete [REDACTED] (b) (4): Per 21CFR201.57: *Additional subsections*. Additional subsections may be included, as appropriate, if sufficient data are available concerning the use of the drug in other specified subpopulations (e.g., renal or hepatic impairment). Additional subsections should not be created if there are no clinically relevant differences in response, safety, or recommendations for use of the drug in that subpopulation compared to the indicated population.
21. Revise Section 10: Remove [REDACTED] (b) (4). Include all text under the main section number.
22. Revise Section 11: Add non-proprietary name. List the inactive ingredients in alphabetical order (see USP General Chapters <1091> Labeling of Inactive Ingredients).
23. Revise the content and format of information found in the Clinical Pharmacology section (Section 12) of labeling to be consistent with FDA Guidance for Industry, "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" (available at <https://go.usa.gov/xn4qB>). Consider strategies to enhance clarity, readability, and comprehension of this information for health care providers through the use of text attributes, tables, and figures as outlined in the above guidance.
24. Revise Section 14 to remove [REDACTED] (b) (4)
25. Do not include a revision date at the end of labeling. The revision date at the end of highlights for products in PLR format replaces the "revision" or "issued" date that appears at the end of labeling in non-PLR format. The revision date is not needed here."

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/s/

VIRGINIA E KWITKOWSKI
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: April 23, 2019
Requesting Office or Division: Division of Hematology Products (DHP)
Application Type and Number: NDA 212320
Product Name and Strength: Accrufer (ferric maltol) capsules 30 mg
Applicant/Sponsor Name: Shield Therapeutics
FDA Received Date: April 15, 2019
OSE RCM #: 2018-2097-1
DMEPA Safety Evaluator: Stephanie DeGraw, PharmD
DMEPA Team Leader: Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Hematology Products requested we review the revised container label and carton labeling for Accrufer (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review^a.

2 CONCLUSION

The revised container label and carton labeling is unacceptable from a medication error perspective. Specifically, we recommend reorganizing the critical information on the principal display panel, revising the storage statement, and revising the “usual dosage” statement. We provide recommendations below for the Sponsor.

^a DeGraw, S. Label and Labeling Review for Accrufer (ferric maltol) NDA 212320. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 MAR 4. RCM No.: 2018-2097.

2.1 RECOMMENDATIONS FOR SHIELD THERAPEUTICS

We recommend the following be implemented prior to approval of this NDA:

A. Container Label and Carton Labeling

1. We note the revisions made to the information on the principal display panel. However, we recommend revising the order of the critical information, so that the established name appears immediately following the proprietary name in accordance with 21 CFR 201.10(g)(1). For example:

Accrufer		Accrufer
(ferric maltol*) capsules	OR	(ferric maltol*)
30 mg		capsules
		30 mg

2. We recommend revising the storage statement to include the missing closed parenthesis after “77°F” and to add the “See controlled room temperature” statement. For example, “Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F). [See USP controlled room temperature].”
3. We note the addition of the “Usual Dosage” statement to the container label. However, we recommend removing ^{(b) (4)} and ^{(b) (4)} from the “Usual Dosage” statement on the carton label per 21 CFR 201.55. Revise to read “Usual Dosage: ^{(b) (4)} twice daily on an empty stomach. See prescribing information.” If space permits on the container label, we recommend adding the longer dosage statement to be consistent with the carton labeling.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON APRIL 15, 2019

Container Label



Carton Labeling



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**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: April 22, 2019

To: Rachel McMullen, MPH, MHA, Senior Regulatory Project Manager,
Division of Hematology Products (DHP)

Virginia Kwitkowski, Associate Director for Labeling, DHP

From: Robert Nguyen, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, MPH, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for Accrufer (ferric maltol) capsules, for oral
use

NDA: 212320

In response to DHP's consult request dated October 25, 2018, OPDP has reviewed the proposed product labeling (PI) and patient package insert (PPI) for the original NDA submission for Accrufer.

PI: OPDP's has reviewed the proposed labeling based on the draft PI received by electronic mail from DHP (Rachel McMullen) on April 9, 2019, and we do not have any comments.

PPI: A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI were sent under separate cover on April 22, 2019.

Thank you for your consult. If you have any questions, please contact Robert Nguyen at (301) 796-0171 or Robert.Nguyen@fda.hhs.gov.

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/s/

ROBERT L NGUYEN
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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: April 22, 2019

To: Anne Farrell, MD
Director
Division of Hematology Products (DHP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Shawna Hutchins, MPH, BSN, RN
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Robert Nguyen, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): ACCRUFER (ferric maltol)

Dosage Form and Route: Capsules, for oral use

Application Type/Number: NDA 212320

Applicant: Shield Therapeutics

1 INTRODUCTION

On September 27, 2018, Shield Therapeutics submitted for the Agency's review an original New Drug Application (NDA) for ACCRUFER (ferric maltol) capsules, for oral use, for the proposed indication of the treatment of iron deficiency in adults.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematology Products (DHP) on October 25, 2018 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for ACCRUFER (ferric maltol) capsules, for oral use.

2 MATERIAL REVIEWED

- Draft ACCRUFER (ferric maltol) PPI received on September 27, 2018 and received by DMPP and OPDP on April 9, 2019.
- Draft ACCRUFER (ferric maltol) Prescribing Information (PI) received on September 27, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 9, 2019.

3 REVIEW METHODS

In 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.

- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

SHAWNA L HUTCHINS
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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: March 4, 2019
Requesting Office or Division: Division of Hematology Products (DHP)
Application Type and Number: NDA 212320
Product Name and Strength: Accrufer (ferric maltol) capsules 30 mg
Product Type: Single Ingredient Product
Rx or OTC: Prescription (Rx)
Applicant/Sponsor Name: Shield Therapeutics
FDA Received Date: September 27, 2018 and January 11, 2019
OSE RCM #: 2018-2097
DMEPA Safety Evaluator: Stephanie DeGraw, PharmD
DMEPA Team Leader: Hina Mehta, PharmD

1. REASON FOR REVIEW

Shield Therapeutics submitted a 505(b)(2) for NDA 212320 Accrufer (ferric maltol) capsules on September 27, 2018 for the treatment of iron deficiency in adults. The Division of Hematology Products (DHP) requested DMEPA evaluate the proposed container labels, carton labeling, and Prescribing Information (PI) for areas of vulnerability that could lead to medication errors.

2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine post-market safety surveillance

3. OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed container label, carton labeling, and prescribing information for Accrufer (ferric maltol) to identify deficiencies that may lead to medication errors and other areas of improvement.

Our review of the proposed PI identified the use of an ambiguous symbol (i.e., hyphen) that may cause confusion in Section 2 *Dosage and Administration*. In addition, we identified areas in the PI, carton labeling and container labels that can be modified to improve the clarity of the information presented.

4. CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed PI and labels can be improved to increase clarity of important information to promote the safe use of the product. We provide recommendations for the division in Section 4.1 and recommendations for Shield Therapeutics in Section 4.2 below.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Highlights of Prescribing Information

1. Dosage and Administration

- a. We recommend revising the first bullet to state the dose (i.e., 30 mg) rather than (b) (4)

2. Dosage Forms and Strengths

- a. We recommend deleting (b) (4) underneath the heading as (b) (4)

B. Section 2 Dosage and Administration

1. 2.1 Recommended Dosage

- a. We recommend revising and combining the first two statements to more clearly and concisely convey the proper dosage and administration information. For example, "The recommended dose of ACCRUFER is 30 mg orally twice daily taken 1 hour before or 2 hours after meals. Do not open, break, or chew capsules."

C. Section 3 Dosage Forms and Strengths

1. We recommend revising this statement read "Capsules: 30 mg iron, as ferric maltol, in red capsules (b) (4) with '30'."

D. Section 16 How Supplied / Storage and Handling

1. 16.1 How Supplied

- a. We recommend revising the first statement to read "30 mg, as ferric maltol: Red capsule (b) (4) with "30"
 - 56 count bottle of 30 mg capsules in HDPE bottles with a child-proof polypropylene push-lock (NDC XXXXXXXXX)."
- b. The NDC is denoted by a placeholder. We recommend requesting the proposed NDC for review.

2. 16.2 Storage

- a. We recommend deleting (b) (4)
- b. To increase readability, a degree sign should follow each numeric temperature value. In addition, we recommend consistency in the inclusion of the unit of measure following each numeric value among the storage information. As currently presented there is inclusion of the unit of measure in the excursion F temperature only.

4.2 RECOMMENDATIONS FOR SHIELD THERAPEUTICS

A. General Comments for the Container Label and Carton Labeling

1. We note the use of a placeholder for the NDC. We request you submit your proposed NDC for review.
2. As currently presented, all information on the principal display panel is of similar size and prominence. We recommend increasing the size of the proprietary name and established name. The proprietary name and established name should be displayed in a manner consistent with FDA regulations, taking into account all pertinent factors, including typography, layout, contrast, and other printing features. When increasing the size of the names, ensure the established name (ferric maltol) is at least half the size of the proprietary name (Accrufer) in accordance with 21 CFR 201.10(g)(2).
3. We recommend only including the proprietary name “Accrufer” and the established name “ferric maltol” for the description of the product on the principal display panel. As such, we recommend removing (b) (4)
4. The strength is not prominent as currently presented and may be interpreted as part of the proprietary name. Therefore, we recommend increasing the prominence of the strength.
5. We recommend adding an asterisk after the established name, for example (ferric maltol)*, and adding a corresponding asterisk before the “each capsule contains” statement to be in alignment with other approved iron-containing products.
6. We recommend removing (b) (4) from the quantity statement and decreasing the size of “56 capsules” as post-marketing experience has shown that the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is of similar prominence to strength statement.
7. As currently presented, the format of the expiration date is not indicated. We recommend that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

8. We recommend adding an address for the manufacturer. This should contain, at a minimum, the city, state, and zip code per 21 CFR 201.1(h)(6)(i).

B. Container Label

1. Replace “Rx” symbol with the statement “Rx only” per Section 503(b)(4)(A) of the Federal Food, Drug, and Cosmetic Act. Additionally, we recommend decreasing the size of the “Rx Only” statement as this information is more prominent than critical information on the principal display panel.
2. Per 21 CFR 201.55, the label requires a “Usual Dosage” statement. If space is limited, the statement may read “Usual Dosage: See prescribing information.”
3. We recommend adding storage information to the container label to ensure this important information is accessible to the end user.

C. Carton Labeling

1. The Drug Supply Chain Security Act (DSCSA) requires certain prescription drugs to have a human-readable and machine-readable (2D data matrix barcode) product identifier on the smallest saleable unit (i.e., the carton) for tracking and tracing purposes. The product identifier contains the NDC, serial number, lot, and expiration date. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act.^a The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product’s labeling.
2. We recommend decreasing the size of the “Rx Only” statement as this information is currently more prominent than critical information on the principal display panel.
3. We recommend removing (b) (4) from the “Usual Dosage” statement per 21 CFR 201.55. Revise to read “(b) (4) twice daily on an empty stomach. See full prescribing information.”
4. We recommend including the recommended temperature range and excursion temperature range as part of the storage statement (i.e., store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F)).

^a <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf>

Additionally, we recommend deleting (b) (4) from the storage information statement as this information is unnecessary.

APPENDICES: METHODS & RESULTS FOR MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Accrufer received on September 27, 2018, from Shield Therapeutics.

Table 2. Relevant Product Information for Accrufer	
Initial Approval Date	N/A
Active Ingredient	ferric maltol
Indication	For the treatment of iron deficiency in adults
Route of Administration	Oral
Dosage Form	Capsules
Strength	30 mg
Dose and Frequency	One capsule (30 mg) twice daily on an empty stomach
How Supplied	30 mg ferric iron (as ferric maltol) hard red capsules are supplied in 56-count bottles
Storage	Controlled room temperature 20 to 25°C (68 to 77°F)
Container Closure	HDPE bottles with a child-proof polypropylene push-lock

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of Failure Mode and Effects Analysis,^b along with post-market medication error data, we reviewed the following Accrufer labels and labeling submitted by Shield Therapeutics:

- Container Label received on September 27, 2018
- Carton Labeling received on September 27, 2018
- Prescribing Information (no image show) received on January 11, 2019.
<\\cdsesub1\evsprod\nda212320\0009\m1\us\114-labeling\draft\labeling\prescribing-information.pdf>

G.2 Labels and Labeling

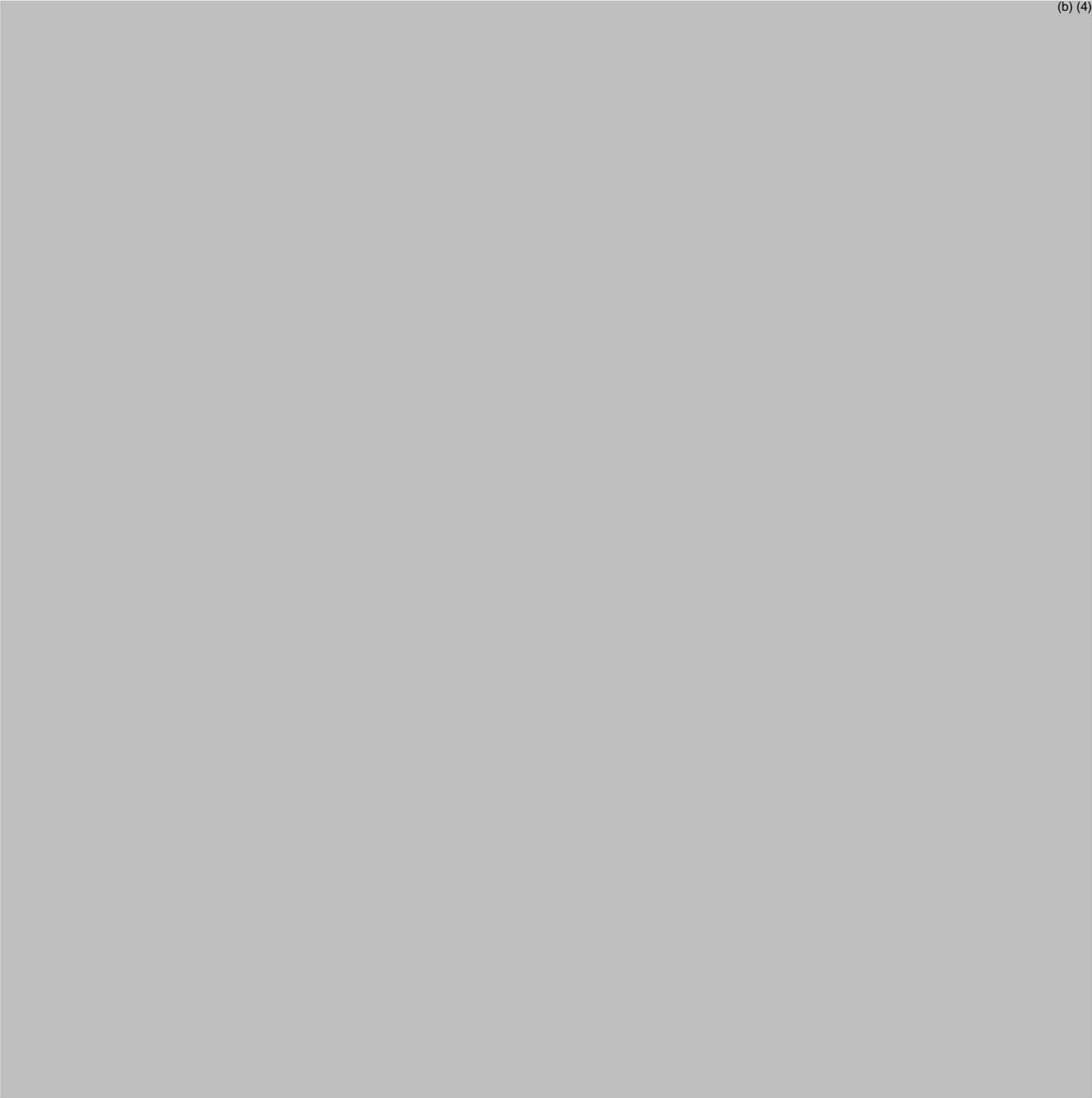
Container Label



^b Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Carton Labeling

(b) (4)



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

/s/

STEPHANIE L DEGRAW
03/04/2019 12:02:41 PM

HINA S MEHTA
03/04/2019 12:41:19 PM