

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

212320Orig1s000

Trade Name: ACCRUFER (ferric maltol) capsules

Generic or Proper Name: ferric maltol

Sponsor: Shield Therapeutics (UK) Ltd.

Approval Date: July 25, 2019

Indication: For the treatment of iron deficiency in adults.

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212320Orig1s000

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APPLICATION NUMBER:

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APPROVAL LETTER

NDA 212320

NDA APPROVAL

Shield Therapeutics (UK) Ltd.
c/o Clinipace Worldwide
Attention: Frank Schmidberger
Regulatory Strategic Development Manager
1434 Spruce Street, Suite 100
Boulder, CO 80302

Dear Mr. Schmidberger:

Please refer to your new drug application (NDA) dated September 27, 2018, received September 27, 2018, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ACCRUFER (ferric maltol) capsules.

This new drug application provides for the use of ACCRUFER (ferric maltol) capsules for the treatment of iron deficiency in adults.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.¹ Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Patient Package Insert) as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.²

The SPL will be accessible via publicly available labeling repositories.

¹ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

² We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the carton and container labeling submitted on May 8, 2019, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission “**Final Printed Carton and Container Labeling for approved NDA 212320.**” Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for Accrufer was not referred to an FDA advisory committee because the safety profile is similar to that of other drugs approved for this indication.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are deferring the submission of your pediatric studies, because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required under section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. These required studies are listed below:

3667-1 Conduct and submit study report and datasets from a study (PK sub-study of ST10-01-305) in pediatric patients with iron deficiency age 1 month to < 10 years for pharmacokinetics (PK) and pharmacodynamics (PD) to confirm the dosing used in the efficacy and safety study.

The timetable you submitted on July 25, 2019, states that you will conduct this study according to the following schedule

Final Protocol: 10/ 2019
Study Completion: 10/2021
Final Report: 01/2022

3667-2 Conduct and submit study report and datasets from a study (ST10-01-103) in pediatric patients with iron deficiency age 10 to 17 years for pharmacokinetics and pharmacodynamics to determine the dosing to be used in an efficacy and safety study.

The timetable you submitted on July 25, 2019, states that you will conduct this study according to the following schedule

Final Report Submission: 08/2019

3667-3 Conduct and submit the study report and datasets from an open-label comparative efficacy and safety study of ST10 and oral ferrous sulfate in infants and children aged 1 month to 17 years with iron deficiency anemia (Study ST10-01-305). Data from PK and PD studies should be utilized to select the doses of ferric maltol for Study ST10-01-305.

The timetable you submitted on July 25, 2019, states that you will conduct this study according to the following schedule

Final Protocol: 10/2019

Study Completion: 10/2021

Final Report Submission: 01/2022

3667-4: Develop a pediatric age appropriate oral formulation and conduct a study to evaluate the bioavailability relative to the capsule formulation in the fasted condition. Subjects should undergo serial blood sampling for serum iron concentration at scheduled intervals during each treatment period. Submit the protocol for review and concurrence prior to commencing.

The timetable you submitted on July 25, 2019, states that you will conduct this study according to the following schedule

Final Protocol: 12/2019

Study Completion: 07/2020

Final Report Submission: 10/2020

3667-5: Evaluate the effect of food on the bioavailability of the pediatric age appropriate oral formulation in healthy adults. Subjects should undergo serial blood sampling for serum iron concentration at scheduled intervals during each treatment period. Submit the protocol for review and concurrence prior to commencing.

The timetable you submitted on July 25, 2019, states that you will conduct this study according to the following schedule

Final Protocol: 12/2019

Study Completion: 12/2020

Final Report Submission: 03/2021

Submit the protocols to your IND 114832, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports please clearly mark your submission, "SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a serious risk of drug-drug interactions between ferric maltol and other oral medications.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following study:

3667-6	Conduct <i>in vitro</i> binding studies to evaluate the potential for ferric maltol to bind commonly used concomitant oral medications. The studies should be performed under conditions that mimic the physicochemical conditions of the gastrointestinal tract. The list of drugs to be evaluated should be inclusive of alendronate, atorvastatin, calcium carbonate, ciprofloxacin, doxycycline, levothyroxine, lisinopril, metoprolol, mycophenolate, and warfarin. The results of this study will identify drugs with significant or potentially clinically meaningful binding that require further <i>in vivo</i> evaluation.
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The timetable you submitted on July 24, 2019, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	08/2019
Final Protocol Submission:	10/2019
Study Completion:	01/2020
Final Report Submission:	01/2020

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

In your protocol include the list of drugs to be evaluated for review and concurrence prior to starting the study. The results of this study will identify drugs with significant or potentially clinically meaningful binding that require further *in vivo* evaluation.

Submit clinical protocol(s) to your IND114832 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

3658-1 Collect and submit multipoint dissolution profiles (5, 10, 15, 20 and 30 minutes) using the FDA's approved dissolution method (USP II (paddle) with sinker, 75 rpm, Tier 1: KCl/HCl Buffer, pH 1.2; Tier 2: KCl/HCl buffer with addition of Pepsin (700,000 to 750,000 unit/L, 900 mL) from newly manufactured commercial batches (minimum of six) and current stability registration batches. Include your proposal for the final acceptance criterion of the dissolution test of ACCRUFER capsules, 30 mg, which setting should be based on the newly collected data. If Tier 1 dissolution fails due to crosslinking, you may proceed to use Tier 2 dissolution testing with Pepsin as per USP. Provide evidence of cross-linking in gelatin capsules. Include photographic documentation or capsule switching test might be used to confirm crosslinking.

The timetable you submitted on June 21, 2019, states that you will conduct this study according to the following schedule:

Final Report Submission: 7/2020

Submit your PMC Final Report under a Prior Approval Supplement (PAS) to the NDA, including the requested dissolution data and proposed final dissolution acceptance criterion, within twelve (12) months from the NDA's action date.

Submit clinical protocols to your IND 114832 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled **"Postmarketing Commitment Protocol," "Postmarketing Commitment Final Report," or "Postmarketing Commitment Correspondence."**

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the Prescribing Information, Medication Guide, and Patient Package Insert (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
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 *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs*.³

³ When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.⁴ Information and Instructions for completing the form can be found at FDA.gov.⁵ For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.⁶

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at FDA.gov.⁷

If you have any questions, call Rachel McMullen, Senior Regulatory Project Manager, at (240) 402-4574.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, MD
Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
 - o Prescribing Information
 - o Patient Package Insert

⁴ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

⁵ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

⁶ <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>

⁷ <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>

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/

ANN T FARRELL
07/25/2019 03:00:22 PM
signing on behalf of Dr. Pazdur