NDA 213036

NDA APPROVAL

Amivas, LLC
c/o Fast Track Drugs and Biologics LLC
Attention: Janet H. Ransom, PhD
President
5 Paramus Court
North Potomac, MD 20878

Dear Dr. Ransom:

Please refer to your new drug application (NDA) dated September 26, 2019, received September 26, 2019, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Artesunate for Injection, 110 mg/vial.

This new drug application provides for the use of Artesunate for Injection for the initial treatment of severe malaria in adult and pediatric patients.

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) 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 enclosed carton and container labeling, 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 213036**." Approval of this submission by FDA is not required before the labeling is used.

MARKET PACKAGE

Please submit one market package of the drug product when it is available to the following address:

Gregory DiBernardo
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 6223
10903 New Hampshire Avenue
Silver Spring, Maryland
Use zip code **20903** *if shipping via United States Postal Service (USPS).*
Use zip code **20993** *if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

ADVISORY COMMITTEE

Your application for Artesunate for Injection was not referred to an FDA advisory committee because outside expertise was not necessary; there were no issues that would benefit from advisory committee discussion.

PROPRIETARY NAME

If you intend to have a proprietary name for this product, the name and its use in the labeling must conform to the specifications under 21 CFR 201.10 and 201.15. We recommend that you submit a request for a proposed proprietary name review. (See the guidance for industry *Contents of a Complete Submission for the Evaluation of Proprietary Names*. and *PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 through 2022*.)

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.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (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 the nonclinical signal of serious risk of pregnancy and maternal complications as well as adverse effects on the fetus, neonate, and infant following exposure to Artesunate for Injection in pregnant women. We have also determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the signals of serious risk of development of resistance to artesunate and dihydroartemisinin (DHA), adverse effects on female fertility, and in vivo genotoxicity.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

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

3851-1 Conduct a single-arm descriptive international study collecting data in women exposed to IV artesunate during pregnancy to assess risk of pregnancy and maternal complications and adverse effects on the fetus, neonate, and infant. Infant outcomes will be assessed through at least the first year of life. The study will collect information for a minimum of 7 years.

The timetable you submitted on May 22, 2020, states that you will conduct this study according to the following schedule:

Draft protocol submission:	11/ 2020
Final protocol submission:	04/ 2021
Interim study report:	04/ 2022
Interim study report:	04/ 2023

Interim study report:	04/ 2024
Interim study report:	04/ 2025
Interim study report:	04/ 2026
Interim study report:	04/ 2027
Study completion:	05/ 2028
Final study report submission:	11/ 2028

3851-2 Conduct a 5-year surveillance study to evaluate the potential development of resistance to artesunate and DHA as obtained from ongoing resistance monitoring programs on antimalarials.

The timetable you submitted on May 22, 2020, states that you will conduct this study according to the following schedule:

Draft protocol submission:	05/ 2021
Final protocol submission:	11/ 2021
Interim study report:	11/ 2022
Interim study report:	11/ 2023
Interim study report:	11/ 2024
Interim study report:	11/ 2025
Interim study report:	11/ 2026
Study completion:	11/ 2026
Final study report submission:	05/ 2027

3851-3 Conduct a female fertility study in rats that tests the adverse effects of intravenous artesunate when administered prior to mating and continued through mating and implantation in accordance with ICH S5(A) and 21 CFR 58 Good Laboratory Practice for Nonclinical Laboratory Studies.

The timetable you submitted on May 22, 2020, states that you will conduct this study according to the following schedule:

Draft protocol submission:	07/ 2020
Final protocol submission:	10/ 2020
Study completion:	07/ 2021
Final study report submission:	10/ 2021

3851-4 Conduct an In Vivo Micronucleus Assay that evaluates intravenous artesunate at doses demonstrated to achieve exposure at the target tissue site(s) and in accordance with the OECD Guideline for the Testing of Chemicals #474 and 21 CFR Part 58 Good Laboratory Practice for Nonclinical Laboratory Studies.

The timetable you submitted on May 22, 2020, states that you will conduct this study according to the following schedule:

Final protocol submission:	06/ 2020
Study completion:	06/ 2020
Final study report submission:	08/ 2020

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit clinical protocol(s) to your IND 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).**

Submitting the protocols for the required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312 or FDA's regulations under 21 CFR parts 50 (Protection of Human Subjects) and 56 (Institutional Review Boards).

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.

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3851-5 Conduct a descriptive 5-year study on the use of Artesunate for Injection in the U.S.

The timetable you submitted on May 22, 2020, states that you will conduct this study according to the following schedule:

Draft protocol submission:	11/ 2020
Final protocol submission:	04/ 2021
Interim study report:	04/ 2022
Interim study report:	04/ 2023
Interim study report:	04/ 2024
Interim study report:	04/ 2025
Study completion:	04/ 2026
Final study report submission:	10/ 2026

3851-6 Conduct a multiple-dose safety, tolerability, pharmacokinetics (PK) study in pediatric patients with severe malaria from 0 to 12 months of age receiving 2.4 mg/kg Artesunate for Injection. The majority of pediatric patients in this age group is to be 6 months of age and younger.

The timetable you submitted on May 22, 2020, states that you will conduct this study according to the following schedule:

Draft protocol submission:	11/ 2020
Final protocol submission:	11/ 2021
Interim study report:	11/ 2022
Interim study report:	11/ 2023
Interim study report:	11/ 2024
Interim study report:	11/ 2025
Study completion:	11/ 2026
Final study report submission:	05/ 2027

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocols to your IND 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. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[4]

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.[5] Information and Instructions for completing the form can be found at 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]

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biological products qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[7] http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm

If you have any questions, call Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-4063.

Sincerely,

{See appended electronic signature page}

John J. Farley, MD, MPH
Acting Director
Office of Infectious Diseases
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
- Carton and Container Labeling

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/

JOHN J FARLEY
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