CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213036Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 213036
Assessment # 3

Drug Product Name	Artesunate for injection (110 mg/vial). Co-packaged with 0.3 M sodium phosphate buffer
Dosage Form	Powder for injection
Strength	110 mg/vial
Route of Administration	IV
Rx/OTC Dispensed	Rx
Applicant	Amivas
US agent, if applicable	Janet H. Ransom, Ph.D.

Submission(s) Assessed	Document Date	Discipline(s) Affected
eCTD 0051	4/27/2020	Quality
eCTD 0054	5/13/2020	Quality

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Katherine Windsor	Suong Tran
Drug Product	George Lunn	Thomas Oliver
Manufacturing	Satheesh Podaralla	Steven Frisbee
Microbiology	Jianli Xue	Neal Sweeney
Biopharmaceutics	Zhuojun Joan Zhao	Elsbeth Chikhale
Regulatory Business Process Manager	Anh-Thy Ly	
Application Technical Lead	Erika Elaine Englund	
Laboratory (OTR)	N/A	
Environmental	Refer to DP review	

QUALITY ASSESSMENT DATA SHEET

IQA NDA Assessment Guide Reference

1. **RELATED/SUPPORTING DOCUMENTS, other documents, consults**
   See reviews #1 and #2

EXECUTIVE SUMMARY

IQA NDA Assessment Guide Reference

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The NDA, as amended, has provided adequate CMC information to assure the identity, strength, purity, and quality of the proposed drug product. The manufacturing and testing facilities for this NDA are deemed acceptable and an overall "Approve" recommendation was entered into Panorama on 05/19/2020. Therefore, this NDA is recommended for approve by the Office of Pharmaceutical Quality (OPQ) at this time**.**

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

This product is indicated for severe malaria, and was granted Fast Track, and Breakthrough Therapy Designation under IND 64769. It is supplied as a single-dose (b) (4) powder for injection that is supplied with a sterile 0.3 M sodium phosphate diluent for constitution.

Proposed Indication(s) including Intended Patient Population	Severe Malaria
Duration of Treatment	0, 12 24 (b) (4) hours, (b) (4)
Maximum Daily Dose	(b) (4)
Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance: Adequate

See Review #1

Drug Product: Adequate

See Review #2

Labeling: Adequate

Labeling recommendations have been communicated to OND PM.

Manufacturing: Adequate

The drug product manufacturing process is comprised of (b) (4) (b) (4) (b) (4) The manufacturing process was found adequate in the previous OPMA review, but a Withhold recommendation was entered due to pending facility issues at (b) (4) Additional CMC information was received on 4/27/2020, and 5/13/2020. The Overall Manufacturing Inspection recommendation was entered as Approve on 5/19/2020. A post-approval inspection is highly recommended for this facility.

This NDA is recommended for approval from an OPMA perspective. For additional details, refer to the review by Satheesh Podaralla.

Biopharmaceutics: Adequate

See Review #1

Microbiology (if applicable): Adequate

Refer to Reviews #1 and #2. The microbiology review #2 recommended this NDA for approval. An addendum to the review clarified that although the sponsor plans to (b) (4) (b) (4)

This NDA is recommended for approval from a microbiology perspective. For additional details, refer to the reviews by Jianli Xue.

C. Risk Assessment- See Review #2

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

None

2. Drug Substance Deficiencies

None

3. Drug Product Deficiencies

None

4. Labeling Deficiencies

None

5. Manufacturing Deficiencies

None

6. Biopharmaceutics Deficiencies

None

7. Microbiology Deficiencies

None

8. Other Deficiencies (Specify discipline, such as Environmental)

None

Application Technical Lead Name and Date:

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Satheesh Podaralla

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Steven Frisbee

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 15 May 2020

TO: **Anh-Thy Ly**
Project Manager
CDER/OPQ/OPRO/DRBPMI/RBPMB1

FROM: **Jianli Xue, Ph.D.**
Review Microbiologist
CDER/OPQ/OPMA/DMA/BII

THROUGH: **Neal J Sweeney, Ph.D.**
Secondary Reviewer
Microbiologist
CDER/OPQ/OPMA/DMA/BII

SUBJECT: NDA: 213036
Submission Date: 8/12/2019
Drug Product: Artesunate/10 mg/mL
Applicant: Amivas, LLC

Microbiology review N213036MR01 addendum.pdf dated 4/17/2020 (page 29/65) documented the sponsor's plan to (b) (4)

(b) (4)

END

Jianli Xue

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Neal Sweeney

Digitally signed by Neal Sweeney
Date: 5/17/2020 03:10:04PM
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/s/

ERIKA E ENGLUND
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U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☐ Approval
☐ Approval with Post-Marketing Commitment
☒ Complete Response

NDA 213036
Assessment # 1

Drug Product Name	Artesunate for injection (110 mg/vial). Co-packaged with 0.3 M sodium phosphate buffer
Dosage Form	Powder for injection
Strength	110 mg/vial
Route of Administration	IV
Rx/OTC Dispensed	Rx
Applicant	Amivas
US agent, if applicable	Janet H. Ransom, Ph.D.

Submission(s) Assessed	Document Date	Discipline(s) Affected
eCTD 0037	2/24/2020	Quality
eCTD 0038	2/24/2020	Quality
eCTD 0036	2/28/2020	Quality
eCTD 0039	2/28/2020	Quality
eCTD 0042	3/4/2020	Quality
eCTD 0045	3/9/2020	Quality
eCTD 0043	3/11/2020	Quality
eCTD 0047	4/10/2020	Quality
eCTD 0050	4/15/2020	Quality

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Katherine Windsor	Suong Tran
Drug Product	George Lunn	Thomas Oliver
Manufacturing	Satheesh Podaralla	Steven Frisbee
Microbiology	Jianli Xue	Neal Sweeney
Biopharmaceutics	Zhuojun Joan Zhao	Elsbeth Chikhale
Regulatory Business Process Manager	Anh-Thy Ly	
Application Technical Lead	Erika Elaine Englund	

Laboratory (OTR)	N/A	
Environmental	Refer to DP review	

QUALITY ASSESSMENT DATA SHEET

IQA NDA Assessment Guide Reference

1. **RELATED/SUPPORTING DOCUMENTS, other documents, consults**
   See review #1

EXECUTIVE SUMMARY

IQA NDA Assessment Guide Reference

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The NDA, as amended, has **not** provided adequate CMC information to assure the identity, strength, purity, and quality of the proposed drug product. The microbiology review previously identified deficiencies with the Container Closure Integrity Test (CCIT) and the drug product review identified a deficiency with the analytical method used in the leachables study. Following review of the IR responses, both the microbiology and drug product reviews are recommending this NDA for approval. The manufacturing and testing facilities for this NDA are not deemed acceptable and an overall "Withhold" recommendation was entered into Panorama on 04/17/2020. Therefore, this NDA is **not** recommended for approve by the Office of Pharmaceutical Quality (OPQ) at this time**.**

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

This product is indicated for severe malaria, and was granted Fast Track, and Breakthrough Therapy Designation under IND 64769. It is supplied as a single-dose (b) (4) powder for injection that is supplied with a sterile 0.3 M sodium phosphate diluent for constitution.

Proposed Indication(s)	Severe Malaria

including Intended Patient Population	
Duration of Treatment	0, 12 24 (b) (4) hours, (b) (4)
Maximum Daily Dose	(b) (4)
Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance: Adequate

See Review #1

Drug Product: Adequate

The drug product consists of 110 mg of sterile (b) (4) artesunate in a 20 mL Type (b) clear glass vial. The vials are reconstituted with 11.0 mL of a sterile 300 mM pH 8.0 sodium phosphate buffer resulting in a final artesunate concentration of 10 mg/mL.

At the time of CMC Review #1, an expiration date had not been proposed. The original storage statement was for (b) (4) (b) (4) (b) (4) The proposed expiration date of 24 months at controlled room temperature on the vials in the cartons was granted.

The stoppers are covered by DMFs, and the stoppers and vials conform to the relevant USP requirements. Leachables were tested using GC-MS and (b) (4) methods. The (b) (4) method lacked adequate sensitivity and for this reason this application was not recommended for approval in CMC Review #1. Revised methods and results were requested and were provided in the 4/15/20 Amendment. A variety of batches of drug product and diluent that had been on stability at 5°C, 25°C/60% RH, and 40°C/75% RH for 7.5-9 months were tested for leachables by HPLC-UV-

MS and GC-MS. No peaks were detected > (b) (4) µg. After discussion with pharm/tox, no safety concerns were identified with these results.

This NDA is recommended for approval from a drug product perspective. For additional details, refer to the review by George Lunn.

Labeling: Adequate

Labeling recommendations have been communicated to OND PM.

Manufacturing: Inadequate

The manufacturing process is comprised of (b) (4)

(b) (4)

(b) (4) The manufacturing process is adequate, but a Withhold recommendation was entered for facilities: (b) (4) (the drug product manufacturer) The Overall Manufacturing Inspection recommendation was WITHHOLD on 4/17/2020

This NDA is recommended for a CR from an OPMA perspective. For additional details, refer to the review by Satheesh Podaralla.

Biopharmaceutics: Adequate

See Review #1

Microbiology (if applicable): Adequate

Review #1 identified deficiencies with the Container Closure Integrity Test (CCIT) for both the drug substance and the drug product, and these deficiencies were sent to the applicant on 2/26/2020. The 3/4/2020 and 4/10/2020 submissions were subsequently reviewed. The results from the container closure integrity testing submitted on 4/10/2020 were found to be acceptable.

This NDA is recommended for approval from a microbiology perspective. For additional details, refer to the reviews by Jianli Xue.

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Sterility	H	H		Acceptable	The microbiology review #2 recommended the NDA for approval
Endotoxin /pyrogen	Raw materials, manufacturing process	M		Acceptable	
Assay, stability	Raw materials, Formulation, manufacturing process	L		Acceptable	
Extractables, leachables	Container closure system	M		Acceptable	The leachables and extractables data was received and found acceptable
Particulate Matter	Raw materials, Formulation, manufacturing process	M		Acceptable	
Reconstitution time	Raw materials, Formulation, manufacturing process	L	(b) (4)	Acceptable	

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

2. Drug Substance Deficiencies

None

3. Drug Product Deficiencies

None

4. Labeling Deficiencies

None

5. Manufacturing Deficiencies

1. During a recent inspection of the (b) (4) drug product manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved. Please list communications submitted to, or held with, the Agency to facilitate resolution of the observed objectionable conditions, or deficiencies, noted at the facility.

6. Biopharmaceutics Deficiencies

None

7. Microbiology Deficiencies

None

8. Other Deficiencies (Specify discipline, such as Environmental)

None

Application Technical Lead Name and Date:

Memo

Re: NDA 213036 Artesunate for Injection from Amivas

From: George Lunn, Ph.D., Drug Product Reviewer

To: Thomas Oliver, Ph.D., Director, Division of New Products I

Date: 21-Apr-2020

Summary: In the drug product review dated 26-Feb-2020 this NDA was not recommended for approval because the analytical methods used to determine leachables were not of sufficient sensitivity. These methods have been modified to increase the sensitivity and leachables testing has been carried out. The results of this testing are satisfactory from the CMC point of view. The PharmTox reviewer concurs with this decision. A more detailed review will be found below in the updated Section P.2.4. In addition, the Section P.8 Stability sections updated with 12 month data will be found below. This NDA is now recommended for approval from the drug product CMC perspective.

Amendments reviewed: 28-Feb-2020, 09-Mar-2020, 11-Mar-2020, 10-Apr-2020, and 15-Apr-2020.

Updated Review Sections

P.2.4 Container Closure System

The container-closure system has not changed over the course of development.

The results for extractables testing are provided in Report IP-GEP 6720GC-b supplied in the Amendment of 11/20/19. (b) (4)

(b) (4)

Leachables have been tested and will continue to be tested. Vials are stored inverted at 5°C and will be tested after 0, 1, 3, 6, 12, and 24 months. Data obtained at 0, 1, and 3 months were provided. Full technical reports were provided in the Amendment of 11/20/19. These testing methods were deemed to lack sensitivity. The advice of the St. Louis FDA laboratory was sought and they performed a paper review of the method and agreed with these conclusions (e-

mail from Cynthia Sommers, OTR of 1/8/20). Therefore revised methods and results were requested and were provided in the Amendment of 4/15/20.

The following batches were tested (storage times are approximate):

Drug product	AR479-156-2691	5°C/9 months	LC-UV-MS
Drug product	AR480C10, AR480C11, AR480C12	40°C/75% RH/7.5 months	LC-UV-MS
Drug product	(b) (4)	(b) (4)	(b) (4)
Diluent	PF537C01	25°C/60% RH/9 months	GC-MS
Diluent	(b) (4)	(b) (4)	(b) (4)

Testing was carried out by (b) (4) The analytical methods are described in reasonable detail and validation details, including Limit of Quantitation, are provided.

(b) (4)
HPLC-UV (b) (4)

HPLC-MS

(b) (4)
LC-MS-UV (b) (4)

GC-MS

In summary (b) (4)
(b) (4)

Comments: Adequate. As initially presented the (b) (4) method lacked sensitivity. (b) (4) The applicant repeated the leachables testing and presented the results in the Amendment of 4/15/20. A variety of batches of drug product and diluent that had been on stability at 5°C, 25°C/60% RH, and 40°C/75% RH for 7.5-9 months were tested for leachables by HPLC-UV-MS and GC-MS. The analytical methods are described in reasonable detail and validation details, including Limit of Quantitation, are provided. In summary (b) (4)
(b) (4)
(b) (4) These conclusions apply both to the vials containing artesunate powder and the vials containing phosphate buffer. See also the PharmTox review which concurs with these conclusions.

P.8 Stability [Artesunate for injection]

P.8.1 Stability Summary and Conclusion and P.8.3 Stability Data

The following stability data are provided for batches manufactured by (b) (4) using semi-synthetic drug substance (as amended in the Amendment of 2/28/20). Each batch of drug product was made from a different batch of drug substance.

Batch	Size	5°C	40°C/75% RH
AR480C10	(b) (4) vials	12 months	6 months
AR480C11	vials	12 months	6 months
AR480C12	vials	12 months	6 months

The following ranges of data are observed.

Test	Specification	5°C	40°C/75% RH
Appearance	Conforms	Conforms	Conforms
Appearance of solution	(b) (4)		
pH			
Water			
(b) (4) constitution time			
Related substances			
Artemisinin			
Dihydroartemisinin			
(b) (4)			
Largest other			
Total			
Assay			
Particulates			
≥ (b) (4) µm			
≥ (b) (4) µm			
Endotoxins*			
Sterility*			

*Measured at initial time point only

The results of photostability testing are buried in a report dealing with stress testing of the bulk drug substance (Amendment of 3/9/20), (b) (4)

(b) (4)

Comments: Adequate. There are no out of specification results and no obvious trends except [redacted] (b) (4) Endotoxins and sterility are measured only at the initial time point. They will be measured at the 12 month time point. An Expiration dating period of 24 months [redacted] (b) (4) is proposed (Amendment of 2/28/20).

The original storage statement was [redacted] (b) (4) (b) (4)

Although the artesunate powder vials are not currently being tested at [redacted] (b) (4) FDA has proposed to the applicant that the product could be stored at room temperature for the following reasons:

- Three batches stored at 40°C/75% RH for 6 months showed no significant degradation (as reported in the NDA).

- Information in the IND for other batches from other manufacturers showed stability at up to 36°C for 36 months.

- The sterile bulk powder has a retest date of [redacted] (b) (4) months when stored at USP controlled room temperature. This is based on 9 months of long-term data for three batches.

The drug product is photosensitive and so the label should contain statements that the vials should be kept the carton until they are about to be used.

In the Amendments of 3/11/20 the applicant agreed to these assessments and changed the storage statements on the vials and cartons to "Store at 20°C to 25°C (59°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from light".

The storage statement in the package insert has been changed to: "Store vials of Artesunate for injection and sterile diluent in the carton at 20°C to 25°C (59°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature]. Do not freeze. Avoid exposure to heat. Do not use beyond the expiration date.

These statements are acceptable. The proposed expiration dating period of 24 months is also acceptable.

P.8 Stability [Phosphate Buffer Solution]

P.8.1 Stability Summary and Conclusion and P.8.3 Stability Data

The following stability data are provided (as amended in the Amendment of 2/28/20).

Batch	Size	25°C/60%	40°C/75%
PF537B01	(b) (4) vials	24 months	24 months
PF537B02	vials	24 months	24 months
PF537C01	vials	12 months	12 months

The following ranges of data are observed. The first column represents the specification limits, the next column the observed values for batches stored at 25°C/60% RH, and the final column the observed values for the batches stored at 40°C/75% RH.

Test	Specification	25°C/60% RH	40°C/75% RH
Appearance	Conforms	Conforms	Conforms
Phosphate content	(b) (4)		
pH			
Particulates			
≥ (b) (4) µm			
≥ (b) (4) µm			
Endotoxins			
Sterility			

An expiration dating period of 36 months is proposed for the buffer when stored at or below 30°C.

Comments: Adequate. There are no out of specification results and no obvious trends. The expiration dating period of 36 months when stored at or below 30°C is reasonable.

The label originally proposed that (b) (4) (b) (4)

FDA recommended that the artesunate powder and buffer be stored in the same carton at USP Controlled Room Temperature. See Section P.8 for the artesunate vials, below, for a fuller explanation.

P.8.2 Postapproval Stability Protocol and Stability Commitment

The following stability testing protocol will be used for the first 3 batches and for one annual batch thereafter.

	Time (months)									
	0	3	6	9	12	18	24	36	48	60
25°C/60%	XYZ	X	X	X	XYZ	X	XYZ	XYZ	XYZ	XYZ

Where X signifies testing for appearance, pH, phosphate assay, and particulates
Y signifies testing for endotoxins
Z signifies testing for sterility

Testing at 48 and 60 months is optional. Annual batches may not be tested at 3 and 9 months.

Comments: Adequate.

George Lunn

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Comments: Satisfactory leachables data Have been supplied and this NDA is now recommended for approval from the drug product point of view. The memo also contains updated stability data.

Thomas Oliver

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Date: 4/21/2020 08:48:55AM
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Comments: Just signed.

CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	213036
Assessment Cycle Number	MR01
Drug Product Name/ Strength	Artesunate/10 mg/mL
Route of Administration	Intravenous
Applicant Name	Amivas, LLC
Therapeutic Classification/ OND Division	OND/OAP/DAIP
Manufacturing Site	Drug substance: (b) (4) (b) (4)
Method of Sterilization	Drug product (sterile powder): (b) (4) (b) (4) Diluent: (b) (4) (b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary:

Document(s) Assessed	Date Received
Original submission	8/12/2019
Quality information	9/26/2019
Quality information	11/14/2019
Quality information	11/20/2019
Quality information	11/27/2019
Quality information	12/16/2019
Quality information	1/3/2020
Quality information	2/4/2020
Quality information	2/24/2020
Quality information	3/4/2020
Quality information	4/10/2020

List Submissions being assessed (table):

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: None

Concise Description of Outstanding Issues: None

Supporting Documents: DMF (b) (4)

(b) (4)

S DRUG SUBSTANCE

S.2. MANUFACTURE

S.2.1 MANUFACTURERS

(b) (4)

S.2.2 DESCRIPTION OF THE MANUFACTURING PROCESS AND PROCESS CONTROLS

The synthesis (b) (4) of artesunate is described in DMF (b) (4)

(b) (4)

(b) (4)

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U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☐ Approval
☐ Approval with Post-Marketing Commitment
☒ Complete Response

NDA 213036
Assessment # 1

Drug Product Name	Artesunate for injection (110 mg/vial). Co-packaged with 0.3 M sodium phosphate buffer
Dosage Form	Powder for injection
Strength	110 mg/vial
Route of Administration	IV
Rx/OTC Dispensed	Rx
Applicant	Amivas
US agent, if applicable	Janet H. Ransom, Ph.D.

Submission(s) Assessed	Document Date	Discipline(s) Affected
eCTD 0001	08/12/2019	Rolling NDA- Part 1
eCTD 0002	09/26/2019	NDA
eCTD 0004	10/07/2019	Corrected 356h form (facilities)
eCTD 0009	11/04/2019	Quality
eCTD 0010	11/14/2019	Quality
eCTD 0012	11/20/2019	Quality
eCTD 0013	11/27/2019	Quality and non-clinical
eCTD 0017	12/16/2019	Quality
eCTD 0018	12/23/2019	Labeling
eCTD 0020	01/03/2020	Quality
eCTD 0022	01/13/2020	Quality
eCTD 0023	01/21/2020	Quality
eCTD 0025	01/22/2020	Quality
eCTD 0026	01/27/2020	Quality
eCTD 0028	01/31/2020	Quality
eCTD 0029	02/04/2020	Quality
eCTD 0031	02/03/2020	Quality
eCTD 0033	02/10/2020	Quality
eCTD 0037	02/24/2020	Quality
eCTD 0038	02/24/2020	Quality

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Katherine Windsor	Suong Tran
Drug Product	George Lunn	Thomas Oliver
Manufacturing	Satheesh Podaralla	Steven Frisbee
Microbiology	Jianli Xue	Neal Sweeney
Biopharmaceutics	Zhuojun Joan Zhao	Elsbeth Chikhale
Regulatory Business Process Manager	Anh-Thy Ly	
Application Technical Lead	Erika Elaine Englund	
Laboratory (OTR)	N/A	
Environmental	Refer to DP review	

QUALITY ASSESSMENT DATA SHEET

IQA NDA Assessment Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II	(b) (4)	(b) (4)	Adequate	1/30/2020	LOA 3/27/2019
	III	Refer to DP review for evaluative of container and applicable DMFs				

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
IND	64769	Intravenous artesunate
IND	76725	Intravenous artesunate

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	NA			

Pharmacology/Toxicology	Refer to tox review			
CDRH-ODE	NA			
CDRH-OC	NA			
Clinical	NA			
Other	NA			

EXECUTIVE SUMMARY

IQA NDA Assessment Guide Reference

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The NDA, as amended, has **not** provided adequate CMC information to assure the identity, strength, purity, and quality of the proposed drug product. The microbiology review identified deficiencies with the Container Closure Integrity Test (CCIT), and an Information Request (IR) was sent. The drug product review identified a deficiency with the analytical method used in the leachables study, and an IR was sent. The manufacturing and testing facilities for this NDA are not deemed acceptable and an overall "Withhold" recommendation was entered into Panorama on 02/25/2020. Therefore, this NDA is **not** recommended for approve by the Office of Pharmaceutical Quality (OPQ) at this time**.**

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

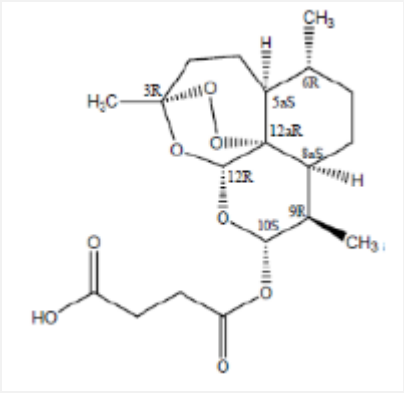
This product is indicated for severe malaria, and was granted Fast Track, and Breakthrough Therapy Designation under IND 64769. It is supplied as a single-dose (b) (4) powder for injection that is supplied with a sterile 0.3 M sodium phosphate diluent for constitution. A CMC dedicated pre-NDA meeting was held between the sponsor and the FDA on June 28, 2019.

Proposed Indication(s) including Intended Patient Population	Severe Malaria

Duration of Treatment	0, 12 24 (b) (4) hours, (b) (4)
Maximum Daily Dose	(b) (4)
Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance: Adequate



The drug substance, artesunate, is a (b) (4) (b) (4)

DMF (b) (4) was found adequate to support this NDA by Katherine Windsor on January 30, 2020. Information in the NDA regarding the (b) (4) (b) (4) (b) (4) Refer also to the microbiology review by Jianli Xue regarding the evaluation of the drug substance (b) (4)

The retest period of the API is (b) (4) months when stored at (b) (4) in the proposed container closure system.

This NDA is recommended for approval from a drug substance perspective. For additional details, refer to the review by Katherine Windsor.

Drug Product: Inadequate

The drug product consists of 110 mg of sterile (b) (4) artesunate in a 20 mL Type (b) clear glass vial sealed with a 20 mm (b) (4) (b) (4) rubber stopper and an aluminum overseal with a (b) (4) (b) (4) 20 mm cap. The vials are reconstituted with 11.0 mL of a sterile 300 mM pH 8.0 sodium phosphate buffer resulting in a final artesunate concentration of 10 mg/mL. Vials of this diluent are supplied along with the vials of artesunate. In-use stability studies were performed at room temperature and 5°C for up to 2 hours. These solutions remain within specification for 1.5 hours and support the label statement of "administer within (b) (4) hour".

A reasonable specification with tests for appearance, appearance of solution, identity, pH, water, (b) (4) constitution time, related substances, vial contents by weight, assay, weight variation, particulates, endotoxins, and sterility is supplied. A justification is provided. The tests generally conform to compendial and ICH recommendations and are supported by the stability data. The analytical methods are USP compendial except for the test for the appearance of the solution which is EP compendial and the HPLC method. The HPLC method is described in the drug substance section. Satisfactory batch analyses are provided for three batches

The stoppers are covered by DMFs that have been reviewed and the stoppers and vials conform to the relevant USP requirements. Leachables are tested using GC-MS and (b) (4) methods. The (b) (4) method lacks adequate sensitivity and for this reason this application is not recommended for approval.

Nine months of stability data obtained at 5°C and 6 months obtained at 40°C/75% RH are supplied for 3 batches. There are no out of specification results and no obvious trends except for (b) (4) (b) (4) **No expiration dating period is currently proposed.** An information request was sent regarding the storage of the product and buffer at room temperature. The expiration dating period will be evaluated following receipt of the response to this IR. Testing of future batches will take place at 25°C/60% RH. As originally stated in the NDA (b) (4) (b) (4) (b) (4) (b) (4) FDA has proposed to the applicant that the vials of artesunate and buffer should be stored together at USP Controlled Room Temperature.

Phosphate Buffer Solution

The diluent consists of 12 mL sterile 300 mM pH 8.0 sodium phosphate buffer in a 20 mL Type (b) clear glass vial sealed with a 20 mm (b) (4) (b) (4) rubber stopper and an aluminum overseal with a (b) (4) (b) (4) 20 mm cap.

The buffer is made from sodium phosphate monobasic monohydrate, and sodium phosphate dibasic anhydrous in water for injection. Sodium hydroxide and phosphoric acid are used for pH adjustment. All of the components are USP/NF compendial and are not novel nor of human or animal origin. They meet the relevant BSE/TSE requirements.

A specification with tests for appearance, identity, volume in container, pH, assay for phosphate, particulates, endotoxins, and sterility is provided. The methods are the USP methods. Satisfactory batch analyses are provided for 3 batches

Satisfactory stability data are provided for 2 batches stored for 24 months and one batch stored for 9 months at both 25°C/60% RH and 40°C/75% RH. Post-approval stability testing will take place at 25°C/60% RH. The expiration dating period of 36 months was found reasonable.

The claim of a categorical exclusion from the requirement to submit an Environmental Assessment is acceptable.

This NDA is recommended for a CR from a drug product perspective. For additional details, refer to the review by George Lunn.

Labeling: Adequate

Labeling recommendations have been communicated to OND PM.

Manufacturing: Inadequate

The manufacturing process is comprised of (b) (4) (b) (4) (b) (4) The manufacturing process is adequate.

There are currently two sites recommended for Withhold: (b) (4) (b) (4) (b) (4) The Overall Manufacturing Inspection recommendation was WITHHOLD on 2/25/2020

This NDA is recommended for a CR from an OPMA perspective. For additional details, refer to the review by Satheesh Podaralla.

Biopharmaceutics: Adequate

NDA 213036 was submitted as a 505(b)(2) NDA under the Federal Food, Drug and Cosmetic Act. The Applicant relies on non-clinical and clinical studies conducted under IND 76725 (owned by the Center for Disease Control and Prevention) and IND 64769 (owned by The Surgeon General, Department of the Army), and published literature on Artesunate (primarily on studies SEAQUAMAT and AGUAMAT) to support efficacy and safety. The Applicant has the right of reference to both IND 64796 and IND 76725.

The proposed dosage form is a powder for solution to be administered via intravenous infusion, only consisting the (b) (4) drug substance, artesunate, without excipients. Because the drug will be fully dissolved prior to administration, there is no need for dissolution testing. The proposed drug is supplied along with a vial containing diluent, 0.3 M Sodium Phosphate, pH 8.0 Buffer.

The totality of evidence for the safety and efficacy of the proposed drug product under this 505(b)(2) application is based on non-clinical and clinical trials conducted with artesunate manufactured for The Surgeon General Department of the Army used under IND 64769 and IND 76725 and artesunate manufactured by the Guilin Pharmaceutical (Shanghai) Co., Ltd. in most literature references. The Applicant has provided sufficient information to justify the reliance of this NDA on the clinical studies described in the literature and studies conducted under IND 64769 and IND 76725.

This NDA is recommended for approval from a biopharmaceutics perspective. For additional details, refer to the review by Joan Zhao.

Microbiology (if applicable): Inadequate

The microbiology review assessed the diluent, drug product and the (b) (4) drug substance (b) (4) DMF (b) (4) was

referenced for the stopper (b) (4) which was last found adequate on 5/6/2019.

The drug product is manufactured by a process that consists of (b) (4) (b) (4)

Regarding the manufacturing process of the diluent, (b) (4) (b) (4)

The review identified deficiencies with the Container Closure Integrity Test (CCIT) for both the drug substance and the drug product, and these deficiencies were sent to the applicant on 2/26/2020.

This NDA is recommended for a CR from a microbiology perspective. For additional details, refer to the review by Jianli Xue.

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Sterility	H	H		Not acceptable	Currently the microbiology review recommends this NDA for CR. This will be re-evaluated upon receipt of the IR concerning CCIT
Endotoxin /pyrogen	Raw materials, manufacturing process	M		Acceptable	

Assay, stability	Raw materials, Formulation, manufacturing process	L		Acceptable	
Extractables, leachables	Container closure system	M		Not acceptable	The LOQ for the test method exceeded the TTC
Particulate Matter	Raw materials, Formulation, manufacturing process	M		Acceptable	
Reconstitution time	Raw materials, Formulation, manufacturing process	L	(b) (4)	Acceptable	

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

2. Drug Substance Deficiencies

None

3. Drug Product Deficiencies

The (b) (4) method for leachables lacks adequate sensitivity and for this reason this application is not recommended for approval.

4. Labeling Deficiencies

None

5. Manufacturing Deficiencies

1. During a recent inspection of the (b) (4) (b) (4)

(b) (4)

2 During a recent inspection of the (b) (4)

(b) (4)

6. Biopharmaceutics Deficiencies

None

7. Microbiology Deficiencies

1. It is acknowledged that container closure integrity test (CCIT) for the proposed container/closure system for the (b) (4) drug substance (b) (4)

(b) (4)

2. It is acknowledged that container closure integrity test (CCIT) for the proposed container/closure system for the subject drug product and the diluent will be performed to include

(b) (4)

8. Other Deficiencies (Specify discipline, such as Environmental)

Application Technical Lead Name and Date:

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Satheesh Podaralla

Digitally signed by Satheesh Podaralla
Date: 2/25/2020 08:58:41PM
GUID: 5b2a8bde0035075366df872da22f1d4a

Steven Frisbee

Digitally signed by Steven Frisbee
Date: 2/25/2020 10:33:27PM
GUID: 54b0011d0005b2d52216cec7d7d58953

CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

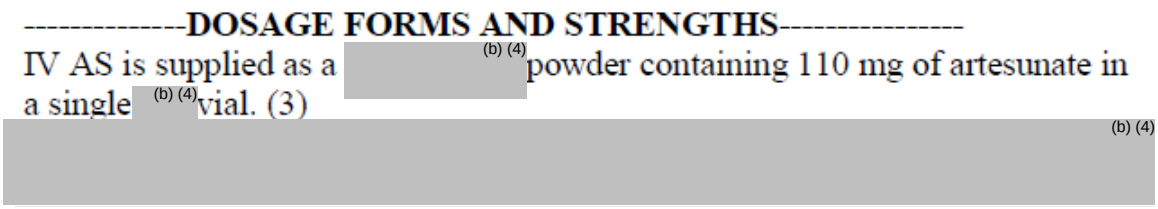
Assessment of Product Quality Related Aspects of the Prescribing Information:

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

Notes: The name should be artesunate for injection (b) (4) and the buffer should generally be referred to as the diluent.

(a) "Highlights" Section (21CFR 201.57(a))

----------DOSAGE FORMS AND STRENGTHS----------



Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	IV AS	Should be artesunate for injection. No proprietary name is being pursued.
Dosage form, route of administration	IV	Should be artesunate for injection
Controlled drug substance symbol (if applicable)	NA	
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths and salt equivalency statement	IV AS is supplied as a sterile white powder containing 110 mg of artesunate in a single use vial. IV AS is supplied with a (b) (4) constitution solution consisting of 12 mL of sterile 0.3 M sodium phosphate, pH 8.0±0.1 buffer.	Recommend: Artesunate for injection 110 mg is supplied in a single-dose vial as a sterile white or almost white powder for constitution with 11 mL of the supplied sterile diluent

(b) "Full Prescribing Information" Section

#2: Section 2 Dosage and Administration (21 CFR 201.57(c)(12))

2 DOSAGE AND ADMINISTRATION

Administer IV AS 2.4 mg/kg intravenously (slow bolus) at 0, 12, 24, (b) (4) hrs, (b) (4) once daily (b) (4) until oral antimalarial medication can be tolerated. (b) (4) (b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Special instructions for product preparation (e.g., (b) (4) constitution, mixing with food, diluting with compatible diluents)	Administer IV AS 2.4 mg/kg intravenously (slow bolus) at 0, 12, 24, (b) (4) hrs, (b) (4) daily (b) (4) until oral antimalarial medication can be tolerated.	Defer to clinical. (b) (4) constitution instructions are currently in Section 16. Name should be artesunate for injection.

 # 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

3 DOSAGE FORMS AND STRENGTHS

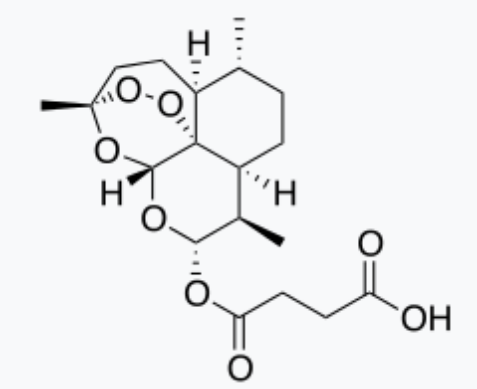
IV AS is supplied as a sterile white powder containing 110 mg of artesunate in a clear glass vial
capped with a rubber stopper and aluminium seal. IV AS is supplied with a (b) (4) constitution solution consisting of 12 mL of sterile 0.3 M sodium phosphate, pH 8.0±0.1 buffer *[see How Supplied/Storage and Handling (16)]*.

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	See above	Suggest: Artesunate for injection 110 mg is supplied as a sterile white or almost white powder in a clear glass vial capped with a rubber stopper and aluminum seal. A (b) (4) constitution diluent consisting of 12 mL of sterile 0.3 M pH 8.0 sodium phosphate buffer is also provided *[see How Supplied/Storage and Handling (16)]*.
Strengths: in metric system and salt equivalency statement	110 mg artesunate	See above
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable. Include "functional score", if present.	white powder containing 110 mg of artesunate in a clear glass vial capped with a rubber stopper and aluminium seal	See above

#11: Description (21CFR 201.57(c)(12))

IV AS contains artesunate [redacted] an antimalarial agent for intravenous administration. The structural formula of artesunate is:

Figure 1: Artesunate Structure



The chemical name of artesunate is 4-Oxo-4-{[(4S,5R,8S,9R,10S,12R,13R)-1,5,9-trimethyl-11,14,15,16-tetraoxatetracyclo[10.3.1.$0^{4,13}$.$0^{8,13}$]hexadec-10-yl]oxy}butanoic acid. Each vial contains 110 mg artesunate [redacted] sterile powder.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	IV AS	Suggestion for first paragraph: Artesunate for injection 110 mg contains artesunate, an antimalarial agent, for intravenous administration. The structural formula is:
Dosage form and route of administration	Intravenous administration	See above
Active moiety expression of strength with equivalence statement for salt (if applicable)	110 mg, (b) (4)	See above
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	A (b) constitution buffer is provided but this is not mentioned in this section	Suggest: Each single-dose vial contains 12 mL of a sterile diluent. Each 11 mL of the sterile diluent that is used for constitution contains 24.1 mg sodium phosphate monobasic monohydrate and 443.6 mg sodium phosphate dibasic anhydrous in water for injection. Sodium hydroxide and phosphoric acid are used to adjust the pH to 7.9-8.1.
Statement of being sterile (if applicable)	Present	See above
Pharmacological/ therapeutic class	antimalarial agent	See above

Chemical name, structural formula, molecular weight	Chemical name and structural formula present. Molecular weight and molecular formula not present	Suggestion for second paragraph: Artesunate is a white or almost white powder with a molecular weight of 384.43. The chemical name is … The empirical formula is $C_{19}H_{28}O_8$. Artesunate for injection is supplied as a white sterile powder for constitution. Each 20 mL glass vial contains 110 mg of artesunate for constitution with 11 mL of the supplied sterile diluent. The constituted solution should be a colorless solution.
If radioactive, statement of important nuclear characteristics.	NA	
Other important chemical or physical properties (such as pKa, solubility, or pH)	None provided	We could add osmolality and pH of (b)(4) constituted solutions. The pH specification for (b)(4) constituted solution is 7.2-7.7 and the measured osmolality is 305-317 mOsm/kg

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

16 HOW SUPPLIED/STORAGE AND HANDLING

IV AS is supplied as a sterile powder for (b)(4) constitution and injection. Each IV AS vial contains 110 mg of AS (in the form of a white or almost white, fine crystalline powder (b) (4) capped with a (b) (4) rubber stopper and aluminum crimp. IV AS is supplied with another glass vial containing 12 mL of sterile 0.3 M sodium phosphate, pH 8.0±0.1 buffer for (b)(4) constitution. Each box contains 4 vials of AS powder and 4 vials of phosphate buffer. (b) (4)

(b) (4)

(b) (4)

(b) (4) Do not freeze. Avoid exposure to heat. Do not use beyond the expiration date.

Reviewer's Comments: This section needs extensive changes which are provided in red and strikeout below. (b) (4)

(b) (4)

Artesunate for injection, 110 mg (b) (4) is supplied as a (b) (4)

(b) (4) white or almost white, sterile, fine crystalline powder for constitution (b) (4)

(b) (4) in single-dose, clear glass vials (b) (4) sealed with a rubber stopper (not made with natural rubber latex) and an aluminum overseal. (b) (4)

(b) (4)

(b) (4)

(b) (4)

Store vials of **artesunate for injection** and sterile diluent in the carton at 20°C to 25°C ((b) (4)°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature]. Do not freeze. Avoid exposure to heat. Do not use beyond the expiration date. [The reasons for this change have been submitted to the applicant.]

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	110 mg	See above
Available units (e.g., bottles of 100 tablets). Include child-resistant closure, induction seal, coil, and desiccant as appropriate.	Each box contains 4 vials of AS powder and 4 vials of phosphate buffer.	See above
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number. Include "functional score", if present.	sterile powder for (b) (4) constitution and injection. Each IV AS vial contains 110 mg of AS (in the form of a white or almost white, fine crystalline powder (b) (4) (b) (4)	See above
Special handling (e.g., protect from light, do not freeze)	Do not freeze. Avoid exposure to heat.	See above
Storage conditions	Store vials of IV AS and Phosphate buffer in the carton between (b) (4) (b) (4) before use. Do not freeze. Avoid exposure to heat. Do not use beyond the expiration date.	See above

Manufacturer/distributor name listed at the end of PI, following Section #17

Manufactured by (b) (4) (b) (4)

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Manufactured by (b) (4) (b) (4)	Adequate

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

No patient labeling

3.0 CARTON AND CONTAINER LABELING

1) Immediate Container Label (Artesunate)

The artesunate label is as follows.

Text as follows:

Far left panel

tear off syringe label
Artesunate
110 mg/11 mL (10 mg/mL)
Date:
Time:
By:

Column 1

NDC XXXXXX-XXX-XX Rx only

Artesunate, sterile powder
for (b) (4) constitution (b) (4)
intravenous injection
110 mg/vial
(b) (4) **vial. Discard unused portion**
Must be (b) (4) constituted with enclosed diluent prior to administration
Use within __ of (b) (4) constitution.

Amivas

Column 2

Each vial contains: Artesunate, 110 mg
Dosage: See full prescribing information for intravenous Artesunate.
Store (b) (4)
Mfg for: Amivas, LLC
1209 Orange St., Wilmington, Delaware19801, USA
Lot No: XXXXXX
Expiry Date: MMMYYYY

[Barcode]

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	**Artesunate, sterile powder for** (b) (4) (b) (4) **intravenous injection**	Should be: Artesunate for injection 110 mg. There is no proprietary name
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4)) and salt equivalency statement (space permitting)	110 mg/vial	Adequate
Route of administration 21.CFR 201.100(b)(3))	**Must be** (b) (4) **constituted with enclosed diluent prior to administration**	Add: by intravenous infusion
Net contents* (21 CFR 201.51(a))	**Each vial contains:** Artesunate, 110 mg	Adequate
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	There are no inactive ingredients in the artesunate vials.	Adequate. Additionally, there is insufficient space for the buffer constituents.
Lot number per 21 CFR 201.18	Present	Adequate
Expiration date per 21 CFR 201.17	Present	DMEPA recommendations for formatting the expiration date should be followed
"Rx only" statement per 21 CFR 201.100(b)(1)	Not present	Should be added
Storage (not required)	Store (b) (4)	Should be changed to conform to the room temperature statement in the PI
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Present	Adequate
Bar Code per 21 CFR 201.25(c)(2)***	Present	Adequate

Name of manufacturer/distributor (21 CFR 201.1)	Mfg for: Amivas, LLC 1209 Orange St., Wilmington, Delaware19801, USA	Adequate, but this is a different entity than the drug product manufacturer which is listed in the package insert
Others	No latex statement **Use within __of (b)(4) constitution** Tear off syringe label provided: tear off syringe label **Artesunate** 110 mg/11 mL (10 mg/mL) Date: Time: By: (b) (4) **vial. Discard unused portion** **Must be (b)(4) constituted with enclosed diluent prior to administration** **Use within __of (b)(4) constitution.**	Ideally a latex statement should be added but there is insufficient space so this may be omitted. Should be single-dose vial. Other statements are acceptable

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ‘‘sample’’, ‘‘physician’s sample’’, or a substantially similar statement and the contents of the package do not exceed 8 grams.
**For solid oral dosage forms, CDER policy provides for exclusion of “oral” from the container label

2) Immediate Container Label (Diluent)

The diluent label is as follows.

Text as follows:

NDC XXXXXX-XXX-XX Rx only

Diluent
For [redacted] Artesunate
[redacted] mL/vial
[redacted] vial
Discard unused portion
Not for direct administration

Amivas

Each vial contains:
0.3 M sodium phospahet buffer solution,
pH 8.0±0.1, [redacted] mL
See accompanying prescribing information
Store [redacted]
Mfg for: Amivas, LLC
1209 Orange St., Wilmington, Delaware19801, USA
Lot No: XXXXXX
Expiry Date: MMMYYYY

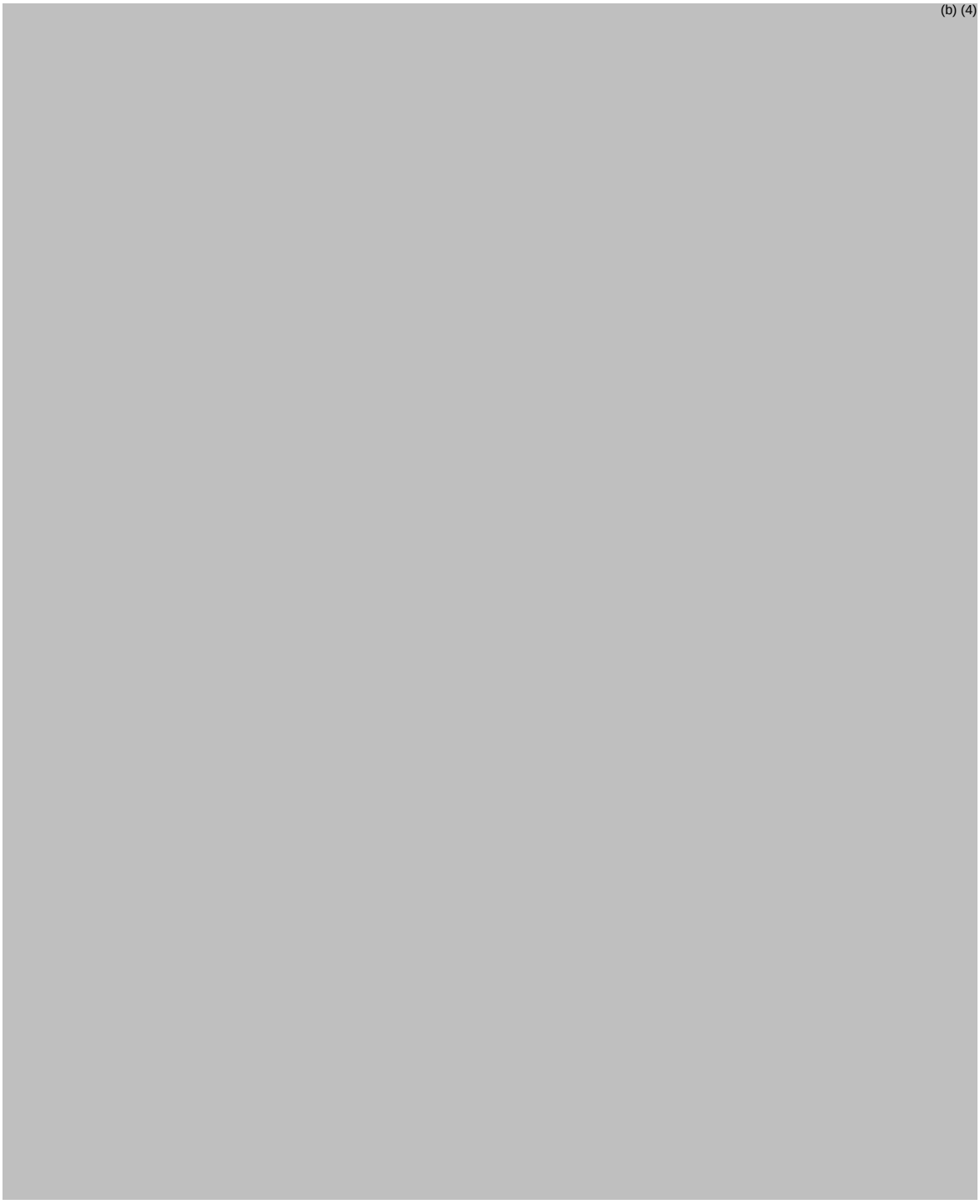
[Barcode]

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	**Diluent** **For use only with Artesunate**	Adequate. No proprietary name proposed
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4)) and salt equivalency statement (space permitting)	**Each vial contains:** 0.3 M sodium phospahet buffer solution, pH 8.0±0.1, (b) (4) mL	Change to: **Each vial contains:** Sterile diluent, 12 mL.
Route of administration 21.CFR 201.100(b)(3))	Not given	Suggest: For the preparation of artesunate solutions for intravenous infusion
Net contents* (21 CFR 201.51(a))	**Each vial contains:** 0.3 M sodium phospahet buffer solution, pH 8.0±0.1, (b) (4) mL	See above
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	Not provided	Suggest: Each single-dose vial contains 12 mL of a sterile diluent. Each 11 mL of the sterile diluent that is used for constitution contains 24.1 mg sodium phosphate monobasic monohydrate and 443.6 mg sodium phosphate dibasic anhydrous in water for injection. Sodium hydroxide and phosphoric acid are used to adjust the pH to 7.9-8.1.
Lot number per 21 CFR 201.18	Present	Adequate
Expiration date per 21 CFR 201.17	Present	Adequate
"Rx only" statement per 21 CFR 201.100(b)(1)	Present	Adequate

Storage (not required)	Store (b) (4)	Should be changed to conform to the room temperature statement in the PI
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Present	Adequate
Bar Code per 21 CFR 201.25(c)(2)***	Present	Adequate
Name of manufacturer/distributor (21 CFR 201.1)	Mfg for: Amivas, LLC 1209 Orange St., Wilmington, Delaware19801, USA	Adequate but this is not the entity named in the package insert
Others	**For use only with Artesunate** (b) (4) **mL/vial** (b) (4) **vial** **Discard unused portion** **Not for direct administration**	(b) (4)

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ‘‘sample’’, ‘‘physician’s sample’’, or a substantially similar statement and the contents of the package do not exceed 8 grams.
**For solid oral dosage forms, CDER policy provides for exclusion of “oral” from the container label

3) Carton Labeling



Text as follows:

Panel 1 Left

NDC XXXXX-XXX-XX Rx only
Artesunate, sterile powder
for (b) (4) constitution and

intravenous injection
110 mg/vial

Panel 1 Right

Lot No: XXXXXX
Expiry date: MMMYYYY
SN: XXXXXXXXX

Panel 2

The contents of the Artesunate vial are to be (b) (4) constituted only with 11.0 mL of supplied sterile 0.3 M sodium phosphate, pH 8.0±0.1 buffer, (b) (4)

Store (b) (4)
Dosage: See full prescribing information for Intravenous Artesunate.

Panel 3 Left

NDC XXXXX-XXX-XX Rx only
Artesunate, (b) (4) for (b) (4) constitution and (b) (4) injection
110 mg/vial

Panel 3 Right

Artesunate, (b) (4)
for (b) (4) constitution and
(b) (4) injection
110 mg/vial

Each carton contains: 4 vials artesunate, 110 mg
and 4 vials sterile diluent for artesunate, (b) (4) mL
(b) (4) vial
The vial stopper is not made with natural rubber latex
Amivas

Panel 4

[Barcode]

Mfg. for Amivas LLC
1209 Orange St, Wilmington, Delaware 19801, USA
Country of Origin: Canada

APPEARS THIS WAY ON ORIGINAL

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	Artesunate, (b) (4) for (b) (4) injection	Suggest: Artesunate for injection 110 mg [No proprietary name]
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2)) and salt equivalency statement	110 mg/vial	See above
Net contents (21 CFR 201.51(a))	Each carton contains: 4 vials artesunate, 110 mg and 4 vials sterile diluent for artesunate, 11 mL	Suggest: Each carton contains: 4 vials of artesunate for injection, 110 mg and 4 vials of sterile diluent (b) (4) 12 mL. The sterile diluent is a 0.3 M pH 8.0 sodium phosphate buffer
Lot number per 21 CFR 201.18	Present	Adequate
Expiration date per 21 CFR 201.17	Present	Adequate
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(d)(2)]	Not present	Suggest: Each single-dose vial contains 12 mL of a sterile diluent. Each 11 mL of the sterile diluent that is used for constitution contains 24.1 mg sodium phosphate monobasic monohydrate and 443.6 mg sodium phosphate dibasic anhydrous in water for injection. Sodium hydroxide and phosphoric acid are used to adjust the pH to 7.9-8.1.

Sterility Information (if applicable)	Deleted per previous recommendation	Add: Sterile
"Rx only" statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)	Present	Adequate
Storage Conditions	Store (b) (4)	Should be changed to conform to the room temperature statement in the PI.
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Present	Adequate
Bar Code per 21 CFR 201.25(c)(2)**	Present	Adequate
Name of manufacturer/distributor	Mfg. for Amivas LLC 1209 Orange St, Wilmington, Delaware 19801, USA	Adequate but this is not the entity on the package insert
"See package insert for dosage information" (21 CFR 201.55)	**Dosage:** See full prescribing information for Intravenous Artesunate	Suggest: See package insert for dosage information
"Keep out of reach of children" (optional for Rx, required for OTC)	Not present	Adequate
Route of Administration (not required for oral, 21 CFR 201.100(d)(1) and (d)(2))	Removed per previous suggestion	Suggest: For intravenous infusion
Latex	The vial stopper is not made with natural rubber latex	Adequate
Others	(b) (4) vial The contents of the Artesunate vial are to be (b) (4) constituted only with 11.0 mL of supplied sterile 0.3 M sodium phosphate, pH 8.0±0.1 buffer, (b) (4)	(b) (4)

Assessment of Carton and Container Labeling: *{Adequate/Inadequate}*

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

ITEMS FOR ADDITIONAL ASSESSMENT

Numerous changes are required as detailed above. The Package Insert on SharePoint has been updated with the recommendations above and recommendations for the vial and container labels will be transmitted as required.

Overall Assessment and Recommendation:

With the changes recommended above the package insert, vial labels, and carton labels are acceptable from the CMC point of view. Labeling negotiations are continuing.

Primary Labeling Assessor Name and Date: George Lunn, Ph.D., 2/26/20

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Thomas Oliver, Ph.D. 2/26/20

George Lunn

Digitally signed by George Lunn
Date: 2/26/2020 01:56:21PM
GUID: 508da72000029f40833369b0a181e8b3

Thomas Oliver

Digitally signed by Thomas Oliver
Date: 2/26/2020 02:06:42PM
GUID: 508da71f00029ed4697700cee3d31ca0
Comments: just signed labeling review!

CHAPTER VI: BIOPHARMACEUTICS

Product Information	
NDA Number	213036
Assessment Cycle Number	#1
Drug Product Name/ Strength	Artesunate powder for IV Solution, 110 mg/vial (co-packaged with a bottle of 12 mL sterile 0.3 M sodium phosphate, pH 8.0 ± 0.1 buffer solution as the diluent)
Route of Administration	Intravenous
Applicant Name	Amivas LLC
Therapeutic Classification/ OND Division	Anti-Infectives/DAI
Proposed Indication	For the initial treatment of severe (b) (4) malaria
Primary Assessors	Zhuojun Joan Zhao, Ph.D.
Secondary Assessors	Elsbeth Chikhale, Ph.D.
Assessment	**Adequate**
Recommendation	Based on the review of the overall information, from a Biopharmaceutics perspective, NDA 213036 for Artesunate powder for IV Solution, 110 mg/vial is recommended for **APPROVAL**.

Assessment Summary:

NDA 213036 was submitted as a 505(b)(2) NDA under the Federal Food, Drug and Cosmetic Act. The Applicant relies on non-clinical and clinical studies conducted under IND 76725 (owned by the Center for Disease Control and Prevention) and IND 64769 (owned by The Surgeon General, Department of the Army), and published literature on Artesunate (primarily on studies SEAQUAMAT[1] and AGUAMAT[2]) to support efficacy and safety. The Applicant has the right of reference to both IND 64796 and IND 76725.

The proposed dosage form is a powder for solution to be administered via intravenous infusion, only consisting the (b) (4) drug substance, artesunate, without excipients. Because the drug will be fully dissolved prior to administration, there is no need for dissolution testing. The proposed drug is supplied along with a vial containing diluent, 0.3 M Sodium Phosphate, pH 8.0 Buffer.

The totality of evidence for the safety and efficacy of the proposed drug product under this 505(b)(2) application is based on non-clinical and clinical trials conducted with artesunate manufactured for The Surgeon General Department of the Army (hereafter

[1] Dondorp, A., et al. (2005). "Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial." Lancet 366(9487): 717-725.

[2] Dondorp, A., et al. (2010). "Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial." Ibid. 376(9753): 1647-1657.

referred to as the "Army Product" used under IND 64769 and IND 76725 and artesunate manufactured by the Guilin Pharmaceutical (Shanghai) Co., Ltd. (hereafter referred to as the "Guilin Product") used in most literature references. The Applicant has provided sufficient information to justify the reliance of this NDA on the clinical studies described in the literature and studies conducted under IND 64769 and IND 76725.

Document(s) Assessed	Date Received
0001 (1)	**August 12, 2019**
0002 (2)	**September 26, 2019**

Highlight Key Issues from Last Cycle and Their Resolution: N/A (This is the first review cycle)

Concise Description of Outstanding Issues: None

B.1 DRUG SUBSTANCE

The drug substance, artesunate, is a (b) (4) (b) (4) (b) (4). The registration batches of the proposed drug product and the proposed commercial Artesunate powder for injection are manufactured using semi-synthetic API, while the clinical drug product described in IND 64769 (owned by The Surgeon General, Department of the Army), the drug product described in IND 76725 (owned by The Center for Disease Control and Prevention (CDC)), and the drug product used in the clinical studies described in the literature were manufactured using (b) (4) API.

Assessment:

The change in the API source from (b) (4) API to semi-synthetic API will be reviewed by the CMC Reviewer and does not affect the Biopharmaceutics evaluation of the proposed drug product. The CMC drug substance reviewer will ensure the equivalence between the (b) (4) API and the semi-synthetic API.

B.2 Drug Product Formulation

The proposed Artesunate for injection is supplied as a sterile powder for (b) (4) constitution and injection, consisting the sterilized, (b) (4) drug substance, artesunate, filled in a 20 mL Type (b) (4) glass vial with a (b) (4) fill of 110 mg/vial. The proposed Artesunate powder for injection contains no excipients. The components/composition of the powder is provided in **Table 1**.

Table 1: Components/Composition of Artesunate Drug Product

Ingredient	Amount		Function
	mg/vial	wt%	
Artesunate, (b) (4) sterile	110	(b) (4)	Active ingredient
Total	110		

The proposed powder is supplied along with a vial containing 12 mL sterile 0.3 M sodium phosphate, pH 8.0 ± 0.1 buffer solution for (b) (4) constitution. The components/composition of the buffer solution is provided in Table 2.

Table 2: Composition of 0.3 M Sodium Phosphate, pH 8.0 Buffer for the commercial product

Ingredient	Amount		Function
	mg/vial	mg/mL	
Monobasic Sodium Phosphate Monohydrate USP	(b) (4)		(b) (4)
Dibasic Sodium Phosphate Anhydrous USP			
Sodium Hydroxide NF		(b) (4)	pH adjustment
Phosphoric Acid NF			pH adjustment
Sterile Water for Injection USP			(b) (4)

B.3 Bridging

Most of the clinical data described in the literature is based on drug product manufactured by Guilin Pharmaceutical (Shanghai) Co., Ltd. (herein "Guilin") that has been administered to millions of patients worldwide, including pediatric patients. The Department of the Army has developed an artesunate formulation that has undergone non-clinical and clinical testing in Army-sponsored clinical trials (IND 64769). The Applicant claims that the Army formulation is bioequivalence to the Guilin formulation as demonstrated in non-clinical (rat and dog) studies and is chemically equivalent to the Guilin formulation. The Applicant claims that these Bioequivalence studies and comparative CMC data have provided the scientific bridge to the large, clinical literature dataset using Guilin drug product to treat malaria. The Applicant, Amivas, is working as the co-development partner to The Surgeon General, Department of the Army, and has submitted NDA 213036 for the drug product developed by the US Army under IND 64769. The same drug product formulation used under IND 64769 is currently distributed by the CDC for civilian, domestic use under protocol CDC-060 (IND 76725) to treat patients in the US who were hospitalized with severe or complicated malaria and for whom IV artesunate was considered to be the optimal treatment. The Applicant has the right of reference to both IND 64796 and IND 76725. More than 600 adult and pediatric patients with severe or complicated malaria have been treated under the CDC's IND 76725. Table 3 below shows the details of the clinical (IND 64769 and IND 76725) and registration batches supporting this NDA.

Table 3:

Batch #	Year of manufacture	Batch size (vials)	DP Manu-facturer	API supplier	API type	API lot number	Processes and Locations	DP Use
14462-16	2004	(b) (4)					(b) (4)	Clinical trials CDC IND 76,725 Study CDC-060 Army IND 64,769 Studies 1128, 1142, 1168, 1263ab
AA241-1-10-01	2010							Clinical trials CDC IND 76,725 Study CDC-060 Army IND 64,769
AR538C01R AR538C02 AR538C03 AR538C04 AR538C05 AR538C06 AR538C07 AR538C08	2018							Clinical trials CDC IND 76,725 Study CDC-060 Army IND 64,769
AR480C10 AR480C11 AR480C12	2018							NDA registration batches

(b) (4)

It should be noted that the Artesunate for injection in the above clinical studies was (b) (4) constituted using a slightly different sterile phosphate buffer (0.3 M, pH 8.1 described in Table 3) compared to the diluent proposed for commercial distribution (described in Table 2).

Table 3: Composition of Sterile Phosphate Buffer Solution, pH 8.1 used in IND 64769[3]

Material	Manufacturer	Amount (Theoretical)
Sodium phosphate, monobasic, USP, (b) (4) Sodium phosphate dibasic USP, (b) (4) Water for Injection, USP qs to Batch Total	(b) (4)	

The concentration of each buffer component in the proposed to be marketed phosphate buffer diluent (Table 2) and the phosphate buffer, pH 8.0 used during the PK/safety/efficacy studies (Table 3) are the same. The Applicant claims that (b) (4)

(b) (4)

[3] DARRTS: IND 064769 REV-QUALITY-03 (General Review), final date 12/20/2004

(b) (4)

Assessment:

To justify reliance on the literature*, the Applicant has submitted a non-clinical bioequivalence study (in rats and dogs) and has provided CMC comparative information between the Guilin drug product (used in most literature studies) and the US Army drug products (proposed drug product). In addition, the Applicant claims that the clinical PK of the US Army formulation and the Guilin formulation are comparable. The non-clinical BE study is reviewed by Dr. Kelly Brant. The comparative CMC information is reviewed by Dr. George Lunn. The pharmacokinetic data of the proposed drug product obtained in the phase 1 studies (1128 and 1142) and phase 2 study (1168)[5] and the comparison of the PK data to the PK data reported in the literature of IV Artesunate are reviewed by Dr. Dakshina Chilukuri. The CMC, non-clinical and clinical pharmacology Reviewers confirmed that the provided data support the bridge between the proposed drug product and the Guilin drug product used in the literature references. Therefore, based on the overall submitted information, reliance on literature studies that used the Guilin drug product is scientifically justified.*

(b) (4)

[redacted]

[5] DARRTS: IND 64769 FRM-TELECON-01 (IND_Telecon), final date 08/08/2006

Zhuojun Zhao

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Elsbeth Chikhale

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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.

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